Management of Pregnancy in a Patient with Severe Hemophilia Type A

Vipra Sharma, MD[1] Aysha Khalid, MD[1] Alice J. Cohen, MD[1]

[1] Department of Hematology Oncology, Newark Beth Israel Medical Center, Newark, New Jersey

Address for correspondence Alice J. Cohen, MD, Newark Beth Israel Medical Center, 201 Lyons Avenue, Newark, NJ 07079 (e-mail: acohen@barnabashealth.org).

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Abstract

Hemophilia type A is a rare inherited bleeding disorder with a diversity of clinical manifestations ranging from persistent bleeding after minor trauma, spontaneous deep muscle or joint hemorrhage, to intracranial hemorrhage. As an X-linked disorder, hemophilia is rare in females and therefore there is little experience with pregnancy and no standardized guidelines to prevent bleeding antepartum, at delivery, and postpartum. We report the clinical course and management of a woman with severe hemophilia A who on two occasions had uncomplicated pregnancies and vaginal deliveries at term utilizing bolus recombinant factor VIII concentrate.

Keywords

- hemophilia A
- pregnancy
- obstetric management
- bolus factor therapy

Hemophilia A and B are the best known of the hereditary bleeding disorders. Hemophilia A and B are X- linked genetic diseases caused by deficiency of clotting factor VIII (FVIII; normal range 62 to 195%) and IX (FIX; normal range 63 to 166%), respectively.[1] Hemophilia A, also called classic hemophilia, occurs in 1 in 5,000 live male births and accounts for 80 to 85% of hemophilia cases. Hemophilia B is far less common, occurring in 1 in 30,000 live births.[2] Hemophilia A and B are prevalent in all ethnic and racial groups. As an X-linked disorder, hemophilia almost exclusively affects males, and females may be heterozygous for the mutation and are referred to as *hemophilia carriers*. Female offspring born to carriers will have 50% chance of being carriers of the disease. Female carriers are expected to have plasma concentration of FVIII or FIX approximately half the concentration of healthy individuals, which can provide adequate hemostasis status.[3] It is estimated that 1 per 100,000 women are symptomatic hemophilia A carriers (FVIII activity levels <30 IU dL^{-1}) and can have a variable range of hemorrhagic manifestations ranging from bleeding or minor trauma to spontaneous hemorrhage. Hemophilia is a rare occurrence in females, accounting for 2.890% of those with hemophilia A, and 4.190% of those with hemophilia B in the United States, according to the Center for Disease Control Universal Data Collection Program.[4] Symptomatic hemophilia can affect females by virtue of the following mechanisms: (1) high degree of lyonization (X chromosome inactivation) of FVIII alleles in carriers; (2) hemizygosity of X chromosome in females with Turner syndrome (XO karyotype); (3) homozygosity in female progeny of hemophilia carriers and affected hemophilic males.[5] In 10 to 20% of carriers, extreme lyonization results in significantly low levels of FVIII and FIX (less than 40 IU dL^{-1}), with an increase in hemorrhagic complications especially in those with very low levels (5 to 10 IU dL^{-1}).[6] Severe hemophilia A (FVIII $<$ 1 IU dL^{-1}), which places a woman at risk for severe bleeding complications, is an extremely rare event.[7]

The hemostatic challenges during pregnancy, childbirth, and puerperium pose a variety of bleeding complications due to invasive prenatal diagnostic and monitoring procedures and the hemostatic challenge of delivery. The information regarding the management and outcomes of females with low FVIII or FIX levels and their fetuses during pregnancy and delivery is limited due to the rarity of the disease.[8] Most of the information is derived from case reports or case series. Only one other case of a pregnant patient with hemophilia has been reported, by Dhar et al, who discussed management of severe hemophilia in pregnancy.[7]

We report our experience of a 28-year-old woman with severe hemophilia A, who had a successful obstetric course with two pregnancies, without hemorrhagic complications.

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Case Report

Patient History

A 28-year-old African-American woman with severe hemophilia A (baseline FVIII activity 0.9 IU dL^{-1}) receiving care at the comprehensive hemophilia treatment center presented with an intrauterine pregnancy at 8 weeks of gestation. Her previous bleeding history included two to three bleeding events per year since childhood, including epistaxis, gingival bleeding, right ankle hemarthroses, and a retroperitoneal hematoma secondary to a ruptured ovarian cyst. Past treatment included fresh frozen plasma, cryoprecipitate, plasma-derived FVIII concentrate, and recombinant FVIII. Blood chromosomal analysis revealed a normal female pattern 46XX with no evidence of sex chromosome mosaicism and a partial inversion of FVIII gene (intron 22) on one of her X chromosomes. Hematologic laboratory evaluation confirmed normal hemoglobin, white blood cell, and platelet count. The comprehensive metabolic panel was within normal limits. Virological tests were negative for HIV, and revealed chronic Hepatitis C, with low viral load. The patient had a history of a miscarriage at 9 weeks 6 months prior to this pregnancy.

First Delivery

Upon presentation, the patient was without any recent bleeding. Her FVIII activity level was 0.94 IU dL^{-1} at baseline and her FVIII inhibitor by Bethesda Assay was negative 4 months prior to her pregnancy. She began prophylaxis with recombinant FVIII concentrate (Recombinate, Baxter Bioscience), at a dose of 40 U kg^{-1} twice weekly starting in her second trimester. At 72 hours her FVIII activity trough level was 7 IU dL^{-1}. Care was coordinated with the high-risk obstetrical team. There were no bleeding complications during the pregnancy.

She was admitted to the hospital for induction of labor at 39 weeks of gestation. The labor was induced at term to ensure adequate control of factor levels and minimize the risks of bleeding. During the labor and delivery period, factor levels were continuously monitored by the laboratory to avoid obstetric complications. Her physical exam was unremarkable, with no evidence of ecchymoses, petechiae, purpura, or vaginal bleeding. On laboratory examination white blood cell count was 7.4×10^9 L^{-1}, hemoglobin 11.6 g dL^{-1}, platelets 249×10^9 L^{-1}, prothrombin time (PT) 14.1 seconds, activated partial thromboplastin time (aPTT) 32 seconds, and FVIII activity of 7 IU dL^{-1}.

The patient received a bolus infusion of Recombinate 50 U kg^{-1} with a 1-hour peak FVIII activity of 111 IU dL^{-1} and an 8-hour trough level of 75 IU dL^{-1}. This was followed by 25 U kg^{-1} every 8 hours intravenously to maintain her FVIII activity level between 50 IU dL^{-1} and 100 IU dL^{-1} until delivery. Labor was induced utilizing Cervidil (Forest Laboratories, New York, NY) and Pitocin (JHP Pharmaceuticals, Rochester, MI).

Morphine, Nubain (EndoPharmaceuticals, Chadds Ford, PA), and Phenergan (Baxter Healthcare Corp., Deerfield, IL) were administered intravenously for analgesia during labor as she refused epidural anesthesia. A female baby was delivered by vaginal delivery after 36 hours of labor with vaginal blood loss of 150 mL. No excessive bleeding was noted during cord clamping. Cord blood sample obtained from the baby revealed FVIII activity of 86 IU dL^{-1}. The patient's postpartum course was uncomplicated and mother and daughter were discharged after 3 days continuing on Recombinate for 6 weeks postpartum. Dosing was as followed: 25 U kg^{-1} every 12 hours days 2 to 5, 25 U kg^{-1} daily days 6 to 14, and 25 U kg^{-1} every other day until cessation of postpartum vaginal spotting at 6 weeks. The patient was slightly anemic at discharge with hemoglobin of 10 g dL^{-1}. A 6-week postpartum Bethesda Assay was negative for an FVIII inhibitor.

Second Delivery

Two years later the patient presented again at 8 weeks of gestation. Her FVIII activity level was 1 IU dL^{-1} at baseline and her FVIII inhibitor by Bethesda Assay was negative. Again prophylaxis with recombinant FVIII concentrate (Recombinate) at a dose of 40 U kg^{-1} twice weekly was started in the second trimester. A 72-hour FVIII activity trough level was 7.8 IU dL^{-1}.

She was admitted for induction of labor at 39 weeks of gestation. Her physical exam showed no evidence of ecchymoses, petechiae, purpura, or vaginal bleeding. On laboratory examination white blood cell count was 7.8×10^9 L^{-1}, hemoglobin 10.5 g dL^{-1}, platelets 267×10^9 L^{-1}, PT 12.5 seconds, and aPTT 39 seconds. Her FVIII activity was 35 IU dL^{-1} at 22 hours after her last treatment. The same protocol of bolus recombinant FVIII concentrate and induction of labor utilized in the first delivery was used in the second delivery. The peak FVIII activity was 105 IU dL^{-1} and an 8-hour trough level was 63 IU dL^{-1}, and her FVIII activity level was maintained between 50 and 100 IU dL^{-1} until delivery.

Intravenous morphine, Nubain, and Phenergan were administered intravenously for analgesia. A female baby was delivered after 20 hours of labor. The total blood loss from the uncomplicated vaginal delivery was 200 mL. There was no excessive bleeding during cord clamping. She experienced minimum postpartum bleeding and the patient and daughter were discharged after 4 days with a hemoglobin of 9.4 g dL^{-1} continuing on Recombinate for 6 weeks postpartum as described post–first delivery.

Discussion

The paucity of reported experience of the obstetric management and outcomes of women with congenital coagulopathies has made management of a pregnant woman with severe hemophilia challenging. Maternal hereditary coagulopathies during pregnancy can have a devastating consequence for both the mother and neonate.

Normal pregnancy is associated with many hemostatic changes with progressive increase in the level of several coagulation factors including fibrinogen FVII, FVIII, FX, FXII, von Willebrand antigen (vWF:Ag) and von Willebrand activity (vWF:Ac). In women with von Willebrand disease (vWD) and carriers of hemophilia A, these levels do not increase until the second trimester, increasing the bleeding risk of women with vWD in early pregnancy but allowing for reduction in

the bleeding tendency at the time of delivery.[9,10] Kadir et al reviewed 84 pregnancies in 31 women with vWD with prepregnancy median levels of FVIII, vWF:Ag and vWF:Ac of 53 IU dL^{-1}, 43 IU dL^{-1}, and 40 IU dL^{-1} respectively. First-trimester vaginal bleeding occurred in 33% of the women as a result of spontaneous miscarriage.[8] Chi and Kadir reviewed 53 female carriers of hemophilia (41 hemophilia A, 12 hemophilia B) who received obstetric care at the Royal Free Hospital between 1995 and 2005. It was found that the mean pregnancy and third-trimester FVIII levels in carriers with hemophilia A were 46 IU dL^{-1} and 121 IU dL^{-1}, respectively. Eight percent of hemophilia A carriers had FVIII levels below 50 IU dL^{-1} and required prophylactic treatment throughout the pregnancy.[11] Unlike women with mild to moderate factor deficiencies, if the hemostatic defect is severe the abnormality will remain during the entirety of the pregnancy. Women with type 3 vWD show very little or no increase in their FVIII and von Willebrand factor plasma levels during pregnancy.[12]

Postpartum hemorrhage (PPH) can be classified as either primary or secondary. Primary PPH is defined as a blood loss of more than 500 mL (or 1000 mL for severe PPH) in the first 24 hours after delivery, and secondary PPH refers to excessive bleeding occurring between 24 hours and 6 weeks postdelivery.[13] Women with hemophilia or other inherited bleeding disorders are at an increased risk of both primary and secondary PPH due to normal physiological decline of pregnancy-induced rise in FVIII and von Willebrand factor especially if levels are < 50 IU dL^{-1} at term.[13] Kadir et al published data on the obstetric problems of hemophilia A and B carriers in a large retrospective study performed at the Royal Free Hospital, London, to assess pregnancy outcome with emphasis on bleeding problems in both mother and fetus.[8] Despite rises in factor levels at term, the incidence of primary and secondary PPH was 22% and 11% in hemophilia carriers as compared with 5 to 8% and 0.8% in the general population.[8] The risk of PPH increases when the prepregnancy FVIII level is below 50 IU dL^{-1}, and this risk persists for several weeks, with reports of hemorrhage up to 3 to 5 weeks postpartum.[3,8] The risk of PPH can be modified with the use of prophylactic treatment to normalize their hemostatic status at delivery and early postpartum, obstetric measures to avoid uterine atony, and a method of delivery with minimal trauma to the genital and perineal region.[14] In women with low factor levels, the aim of prophylaxis therapy outlined by Chi et al is to raise factor levels to above 50 IU dL^{-1} for FVIII, FIX, vWF:Ag, and vWF:Ac or to 70 IU dL^{-1} for FXI for vaginal delivery or cesarean section.[14]

Regional analgesia is an effective method for pain relief for labor pain. However, the use of regional blocks in women with bleeding disorders has been very controversial. It has been suggested that if the hemostatic defect is corrected with replacement therapy or pregnancy-induced factor correction, with factor levels above 50 IU dL^{-1}, an epidural catheter can be placed.[15] In a retrospective series by Chi et al, 80 women with various inherited bleeding disorders had a regional block performed successfully in 41 pregnancies.[16] Only in 10 instances was prophylaxis used, and the remaining with known bleeding disorders normalized clotting factor levels spontaneously during pregnancy. The complications were comparable to the general population and included inadequate anesthesia/analgesia, bloody tap, hypotension, and dural puncture.[16] There were no complications with permanent sequelae. Type 1 vWD patients have undergone safe epidural anesthesia if the FVIII and von Willebrand factor activity levels have risen to levels above 50 IU dL^{-1}.[17]

A male offspring of women who are carriers of hemophilia has a 50% chance of having hemophilia, which should be a consideration in planning the mode of delivery. There is still much discussion on the optimal management of delivery in patients with hemophilia with a fetus affected with more than mild disease due to the potential hemorrhagic complications. Ljung et al reviewed the method of delivery in 117 children with moderate to severe hemophilia born in Sweden between 1970 and 1990.[18] They found 23 occurrences of neonatal bleeding associated with delivery. The incidence of neonatal cranial hemorrhage was 3% (3/87) with vaginal delivery, 64% (11/17) with vacuum extraction, and 15% (2/13) with cesarean section.[18] The data demonstrated that there is a slight risk of serious bleeding during normal vaginal delivery; however, delivery by cesarean section does not eliminate that risk.[18] The management of delivery depends on the hemostatic status of the mother and fetus. Delivery should be performed by the least traumatic method, avoiding prolonged labor and instrumental deliveries with forceps and vacuum extraction.[18]

In a single case report, Dhar et al discussed their experience with the management of a woman with severe hemophilia A (FVIII levels < 1 IU dL^{-1}) who received prophylaxis with 30 U kg^{-1} of recombinant FVIII concentrate (Helixate FS, Aventis Behring) once or twice per week without hemorrhagic complications including safe amniocentesis. At term the patient had spontaneous labor and received continuous infusion of recombinant FVIII at a rate of 3 U kg^{-1} per hour with placement of an epidural catheter and vaginal delivery with no hemorrhagic complications. Continuous infusion of FVIII concentrate was maintained for 48 hours and then bolus prophylaxis for 6 weeks without excessive PPH.[7] Drawing from these successful experiences, it can be concluded that a patient with hemophilia can have a regional block provided the patient has adequate replacement therapy.

The patient presented in this report underwent a vaginal delivery utilizing bolus FVIII concentrate both for prophylaxis (twice weekly 40 U kg^{-1}) and for the management of labor without antepartum or significant PPH. Peak levels of 100 IU dL^{-1} were achieved and trough levels were maintained during labor at greater than 50 IU dL^{-1}. This patient's two successful deliveries demonstrate that bleeding can be minimized with bolus therapy and monitoring of peak and trough FVIII levels. As in the previous case, prophylaxis for 6 weeks postpartum prevented significant PPH. Scheduled induction of labor ensured that members of the hematology, obstetrics, and neonatology departments and special coagulation laboratory were available. Our patient refused epidural anesthesia and therefore the safety of bolus management of epidural anesthesia could not be determined.

Maternal hereditary coagulopathies during pregnancy can have devastating consequences if managed inappropriately during antepartum, intrapartum, and postpartum period. Women with hemophilia present a unique challenge to the obstetrician. Most importantly, as demonstrated by the uncomplicated management of this patient with a rare and severe bleeding disorder, multidisciplinary planning and coordination of care and timely communication between hematologist and obstetrics are critical in ensuring an optimal outcome. Women with a family history of a bleeding disorder, personal history of bleeding (menorrhagia, mucous membrane bleeding, bleeding post–dental extraction, postoperative bleeding, and PPH) or a prolonged aPTT should be screened for hemophilia by measuring coagulation factor levels during family planning visits or at presentation for antenatal care. Identification of affected women or carrier status should prompt counseling and genetic testing prior to conception and determination of fetal gender is essential for management of the child at delivery time. The availability of laboratory support and FVIII concentrate are essential to the safe management of pregnant women with hemophilia.

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