Case Report

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# Surgical management of endometriosis in a severe Hemophilia A female patient and the role of transfusion medicine specialist: A case report with review of literature

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**Abstract:**

Hemophilia A is an X-linked recessive bleeding disorder occurs due to deficiency of factor VIII (FVIII). The disease manifests exclusively in males though it rarely occurs in females due to complex pathophysiological mechanisms. We present a rare case of female hemophilia due to skewed X-inactivation which adversely affected the quality of patient life. She presented with recurrent abdominal pain and was diagnosed with severe endometriosis and underwent total abdominal hysterectomy with left salpingo-oophorectomy and appendicectomy. She was infused recombinant factor VIII both prophylactically and postoperatively as per the World Federation of Hemophilia guidelines. Recombinant Factor VIII was supplemented every 12th hourly and Factor VIII activity levels were monitored daily. She was discharged uneventfully on the postoperative day 21 after screened negative for acquired inhibitors.

**Keywords:**

Hemophilia A, inherited bleeding disorder, recombinant factor VIII, skewed X-inactivation

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## Introduction

Hemophilia A is a hereditary coagulation disorder caused by the deficiency of the Factor VIII, a classic X-linked recessive inheritance that occurs due to the mutations in the FVIII gene, situated on chromosome Xq28 that spans 186 kb.[1] This disorder exhibits a wide range of bleeding manifestations ranging from mild mucocutaneous bleeding to severe life-threatening internal bleeds. Hemophilia A can be classified into mild, moderate, and severe depending upon the factor VIII activity in blood.[2] Normal factor VIII activity in human plasma ranges from 50% to 150%. Severe hemophiliacs are those with factor VIII <1%, moderate and mild hemophiliacs have an F-VIII activity of 1%–4% and 5%–30%, respectively.[3]

Males (XY) are almost exclusively affected with an incidence of 1/5000 birth.[4] The disease is a rare phenomenon in females (XX) as most of them will be silent carriers. We present a case of female severe hemophilia A patient who was surgically treated in our hospital for endometriosis.

## Case Report

A 24-year-old unmarried female, who was a known case of severe hemophilia A and hepatitis B, presented to the gynecology outpatient department with abdominal distention and abdominal pain of 3 days duration with increasing severity. On



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general examination, she was thin built with a bodyweight of 45 kg; febrile and anemic. She had stable vitals, BP of 136/70 mm Hg, and pulse rate of 80/min. There was no visible mass on abdominal examination but generalized tenderness with guarding and rigidity was present.

The family history suggested a hereditary bleeding disorder [Figure 1]. She was born out of a non-consanguineous marriage and had recurrent bleeding episodes since childhood. She was previously diagnosed to have severe hemophilia A due to skewed lyonization in another tertiary care center few years ago while admitted for endometriosis and later underwent laparotomy and right salpingo-oophorectomy. The patient had multiple transfusions of fresh frozen plasmas, cryoprecipitate, and recombinant factor VIII concentrates in the past.

On admission, aPTT was 75.5 s which got corrected by mixing with pooled normal plasma (34 s) and FVIII activity was <1%. Other laboratory parameters were normal [Table 1]. Ultrasound and magnetic resonance imaging of the abdomen suggested features of the left ovarian endometriotic cyst with hematosalpinx and subacute hematoma superior to the bladder and uterus.

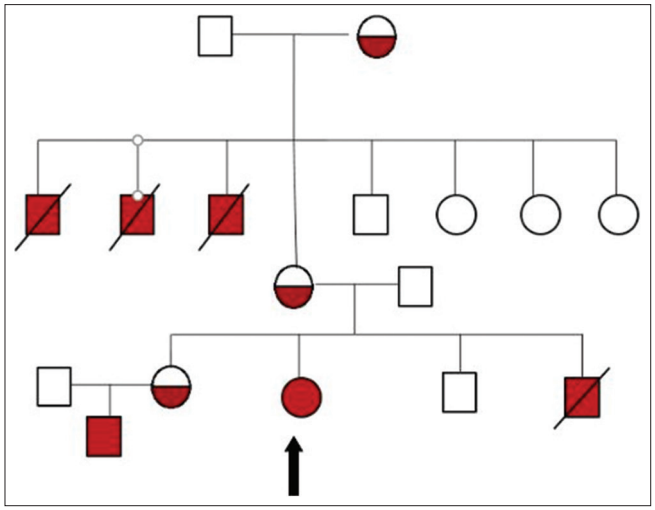

**Figure 1:** Pedigree chart of the patient

Due to severe recurrent Stage IV endometriosis, total abdominal hysterectomy with left salpingo-oophorectomy and appendicectomy was planned after obtaining informed consent from the patient. The procedure was planned by a multidisciplinary team consisting of gynecologists, anesthetists, and transfusion medicine specialists. Our target of factor VIII activity was 100% on the day of surgery; 80% for the next 72 h, 70% for the next 4 days, 60% for the next week, and 50% for the rest of the days. Factor replacement was calculated using the standard formula; ([Desired–Observed factor VIII level] × bodyweight × 0.5) and we maintained a liberal cut-off for factor VIII more than the upper limit of the World Federation of Hemophilia guidelines.[5] Recombinant factor VIII (ELOCTATE®) was provided free of cost from hemophilia society after establishing the absence of FVIII inhibitors. She was infused a prophylaxis dosage of 2250 IU (2.25 ml) of ELOCTATE® as slow IV infusion and factor activity elevated to 103% preoperatively. Intraoperatively, there was a large hemorrhagic chocolate cyst left ovary lying ruptured with extensive pelvic adhesions. She had received one unit of ABO matched crossmatch compatible packed red cell transfusion during surgery. Surgery was done successfully following which ELOCTATE® was administered twice daily, 12 h apart. Factor activity was monitored daily morning which was free of cost and aPTT twice daily prior to the administration of ELOCTATE® and the dose was adjusted accordingly [Table 2]. Her course throughout the hospital was uneventful and was discharged after screened negative for inhibitors.

## Discussion

Hemophilia being an X-linked recessive disorder is more likely to manifest in males. Although it is hereditary, the disease can also occur due to spontaneous mutation of FVIII gene. Type of mutation is crucial in determining the severity of the disease. Some mutations will only decrease the amount of factor VIII but others solely abolish its functional activity. By virtue of the inheritance, pattern females will always be the carriers. However, the clinical demonstration of the

**Table 1: Laboratory parameters of the patient over the course of hospital stay**

| Laboratory investigations | Laboratory reference range | Preoperative day 0 | Postoperative day 0 | Postoperative day 1 | Postoperative days 2 | At discharge |
|---|---|---|---|---|---|---|
| Hb (g/dl) | 12-15 | 10.2 | 9.7 | 9.6 | 9.3 | 9.2 |
| Total leukocyte count (cell/cumm) | 4000-10,000 | 9800 | 10,100 | 10,110 | 10,330 | 9500 |
| Platelet count ($10^3$/cumm) | 150-400 | 320 | 315 | 280 | 318 | 320 |
| Total bilirubin (mg/dL) | 0.2-1 | 0.8 | 0.7 | - | - | 0.8 |
| Serum sodium (mmol/L) | 136-145 | 137 | 138 | - | - | 138 |
| Serum potassium (mmol/L) | 3.5-5.1 | 4 | 4.1 | - | - | 4.2 |
| Blood urea (mg/dL) | 6-20 | 14.5 | 15 | - | - | 15.5 |
| Serum creatinine (mg/dL) | 0.6-1.3 | 0.70 | 0.8 | - | - | 0.8 |

Hb: Hemoglobin

**Table 2: Daily activated partial thromboplastin time, factor VIII activity, and infused recombinant factor over 3 weeks of hospital stay**

| Days | Timings | aPTT (s) | Factor VIII activity[i] (%) | Factor VIII given (IU) |
|---|---|---|---|---|
| Day 0 | 10 am | 73.8 | <1 | 2250 |
| | 10 pm | 52.5 | | 945 |
| Day 1 | 8 am | 48.9 | 38 | 945 |
| | 8 pm | 49.9 | | 945 |
| Day 2 | 8 am | 50.5 | 35 | 1013 |
| | 8 pm | 48.2 | | 1013 |
| Day 4 | 8 am | 49.3 | 37 | 742 |
| | 8 pm | 50.3 | | 742 |
| Day 6 | 8 am | 47.8 | 38 | 720 |
| | 8 pm | 48.3 | | 720 |
| Day 8 | 8 am | 51.5 | 35 | 563 |
| | 8 pm | 49.8 | | 563 |
| Day 10 | 8 am | 48.3 | 38 | 495 |
| | 8 pm | 47.2 | | 495 |
| Day 14 | 8 am | 48.3 | 37.5 | 506 |
| | 8 pm | 46.4 | | 506 |
| Day 16 | 8 am | 46.3 | 40 | 225 |
| | 8 pm | 45.2 | | 225 |
| Day 18 | 8 am | 47.2 | 38 | 270 |
| | 8 pm | 50.7 | | 270 |
| Day 21 | 8 am | 47.2 | 40 | 225 |
| | 8 pm | 49.9 | | 225 |

[i]Factor VIII activity was measured prior to the factor VIII administration.
aPTT: Activated partial thromboplastin time

**Table 3: Review of literature of various inherited female hemophilia A**

| Author | Year | Type of hemophilia | Procedure |
|---|---|---|---|
| Valleix *et al.* | 2002 | Mild-moderate | - |
| Dhar *et al.* | 2003 | Severe | Normal labor |
| Cai SH *et al.* | 2006 | Moderate | - |
| Renault *et al.* | 2007 | Moderate | - |
| Vencasis A *et al.* | 2008 | Severe | - |
| Pavlova A *et al.* | 2009 | Mild-moderate | - |
| Salcus M *et al.* | 2010 | Mild/moderate | - |
| Sharma *et al.* | 2012 | Severe | Normal labor |
| Nair SP *et al.* | 2012 | Moderate | - |
| Zheng A *et al.* | 2015 | Severe | Bleeding |
| Kitamura *et al.* | 2018 | Mild | Subdural hemorrhage |
| Kanda A *et al.* | 2019 | Mild | Total hip arthroplasty |

disease can rarely happen due to diverse mechanisms including homozygosity for mutant allele, selective or skewed inactivation of the normal X chromosome, and 45 X chromosomal constitution.[6]

## X chromosome inactivation

XCI is a phenomenon in which one X chromosome in every female (XX) is transcriptionally silenced for which X-Inactive-Specific Transcript is required.[7] This process is totally random and independent in each cell. It happens during the 8–16 cell progenitor stage in a paternally or maternally derived X chromosome. In normal females, the ratio of maternally and paternally active cells is nearly 1:1 (50:50). In recessive disorders, females tend to be carriers because of the presence of two sets of somatically active genes.

## Skewed X inactivation/lyonization

Non-random inactivation of X chromosome can happen by chance or modulated by genes. These non-random inactivation is also known as skewed X inactivation which is always pathological.[8] When the ratio of selective inactivation is more than 80:20, it is called skewed X-inactivation, which means >80% of cells have one allele being found on the active X chromosome. In this, a female can express defective F8 gene in >80% of the cells and hence the severe disease manifestation can occur.

Dhar *et al.* and Sharma *et al.* reported successful management of normal vaginal delivery in severe female hemophiliacs with prophylaxis dosage of 30 and 40 IU/Kg twice weekly, respectively, followed by 3 IU/Kg during delivery and 48 h postpartum,[9,10] Review of literatures on various inherited female hemophilia cases is listed in Table 3.

# Conclusion

Severe hemophilia A in females is a rare but debilitating disease. Attaining hemostasis in a major surgical procedure is a multidisciplinary approach and can be a unique challenge to the team. Unlike males, managing female patients can be difficult due to menorrhagia and endometriosis. These patients can be put on Factor VIII prophylaxis to reduce the frequency of bleeds and to improve the quality of life.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that her name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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