American Journal of Perinatology Reports

Acquired Hemophilia A: A rare, acquired coagulopathy in the postpartum setting


Affiliations below.

DOI: 10.1055/a-2198-7888


Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:

Background
Postpartum hemorrhage (PPH) remains a leading cause of maternal morbidity. Pregnancy-associated acquired hemophilia A (AHA) caused by autoantibodies against factor VIII can present with recurrent episodes of postpartum bleeding.

Case(s)
Case 1: 50-year-old P0112 with vaginal bleeding 22 days post-cesarean. She underwent dilation and curettage, hysterectomy, and interventional radiology (IR) embolization before AHA diagnosis. She was hospitalized 32 days and received 23 units of blood product. She remains without relapse of AHA after 5 years.

Case 2: 48-year-old P1 with vaginal bleeding eight days post-cesarean. She underwent three surgeries and IR embolization before AHA diagnosis. She was hospitalized 18 days and received 39 units of blood product. Prednisone and cyclophosphamide were continued after discharge.

Conclusions
AHA is a rare cause of PPH. An isolated prolonged aPTT should prompt further workup in postpartum patients with refractory bleeding. Rapid recognition of AHA can prevent significant morbidity related to hemorrhage, massive transfusion, and multiple surgeries.

Corresponding Author:
Dr. Austin Oberlin, Columbia University Irving Medical Center, Obstetrics and Gynecology, 622 West 168th Street, 10032-3784 New York, United States, austin.m.oberlin@gmail.com

Affiliations:
Austin Oberlin, Columbia University Irving Medical Center, Obstetrics and Gynecology, New York, United States
Nicole Krenitsky, Columbia University Irving Medical Center, Division of Maternal-Fetal Medicine, Obstetrics and Gynecology, New York, United States
Christy Gandhi, Columbia University Irving Medical Center, Division of Maternal Fetal Medicine, Obstetrics and Gynecology, New York, United States
[...]
Mary D’Alton, Columbia University Irving Medical Center, Obstetrics and Gynecology, New York, United States

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Acquired Hemophilia A: A rare, acquired coagulopathy in the postpartum setting

Austin Oberlin MD\textsuperscript{1}, Nicole M. Krenitsky MD MBA\textsuperscript{2}, Christy Gandhi MD\textsuperscript{2}, Imo Joseph Akpan MD\textsuperscript{3}, Andrew Eisenberger MD\textsuperscript{3}, Ruth Landau MD\textsuperscript{4}, Ladin Yurteri-Kaplan MD MS\textsuperscript{5}, Lisa Nathan MD\textsuperscript{2}, Jean-Ju Sheen MD\textsuperscript{2}, Anita LaSala MD\textsuperscript{2}, Mary D'Alton MD\textsuperscript{2}

\textsuperscript{1}Department of Obstetrics and Gynecology, Columbia University Irving Medical Center; New York, NY
\textsuperscript{2}Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Columbia University Irving Medical Center; New York, NY
\textsuperscript{3}Division of Hematology and Oncology, Department of Medicine, Columbia University Irving Medical Center; New York, NY
\textsuperscript{4}Department of Anesthesia, Columbia University Irving Medical Center; New York, NY
\textsuperscript{5}Division of Gynecologic Specialty Surgery, Department of Obstetrics and Gynecology, Columbia University Irving Medical Center; New York, NY

Disclosures: Dr. D’Alton has had a leadership role in ACOG II’s Safe Motherhood Initiative which has received unrestricted funding from Merck for Mothers. The other authors did not report any potential conflicts of interest.

Funding: None

Key Words: Postpartum hemorrhage, Bleeding disorder, Coagulopathy, Maternal morbidity

Abstract
Background

Postpartum hemorrhage (PPH) remains a leading cause of maternal morbidity. Pregnancy-associated acquired hemophilia A (AHA) caused by autoantibodies against factor VIII can present with recurrent episodes of postpartum bleeding.

Case(s)

Case 1: 50-year-old P0112 with vaginal bleeding 22 days post-cesarean. She underwent dilation and curettage, hysterectomy, and interventional radiology (IR) embolization before AHA diagnosis. She was hospitalized 32 days and received 23 units of blood product. She remains without relapse of AHA after 5 years.

Case 2: 48-year-old P1 with vaginal bleeding eight days post-cesarean. She underwent three surgeries and IR embolization before AHA diagnosis. She was hospitalized 18 days and received 39 units of blood product. Prednisone and cyclophosphamide were continued after discharge.

Conclusions

AHA is a rare cause of PPH. An isolated prolonged aPTT should prompt further workup in postpartum patients with refractory bleeding. Rapid recognition of AHA can prevent significant morbidity related to hemorrhage, massive transfusion, and multiple surgeries.

Introduction

Postpartum hemorrhage (PPH) remains a leading cause of maternal mortality worldwide. (1) Although the most common causes are uterine atony, obstetric laceration, or retained placenta, recurrent episodes of hemorrhage despite multiple surgical and pharmacologic interventions should elicit consideration of rarer etiologies, including coagulopathies.
Here we present two cases of acquired hemophilia A (AHA) diagnosed in the setting of PPH at a single institution. Both patients provided written consent for publication. In addition, we review the literature on pregnancy-associated AHA including the workup and management for the obstetrician.

Case 1

A 50-year-old G2P0010 with dichorionic diamniotic twins was admitted at 29 weeks gestation with concern for placental abruption and underwent an uncomplicated low-transverse cesarean delivery at 31 weeks in the setting of ongoing vaginal bleeding. She had no history of any bleeding disorder. The patient re-presented on postoperative day 22 with ongoing vaginal bleeding and symptomatic anemia with a hemoglobin of 6.2 g/dL and platelets of 600,000 per mcL. She underwent a suction dilation and curettage during which a uterine scar dehiscence was suspected, and a three cm defect was repaired laparoscopically. After this initial re-operation, her hemoglobin steadily decreased with moderate vaginal bleeding. On day 25, hemoperitoneum was noted on ultrasound and she underwent an exploratory laparotomy, supracervical hysterectomy and evacuation of several liters of hemoperitoneum. Generalized oozing was noted at all surgical sites including peritoneal and skin incisions. Intraoperative PT and aPTT were prolonged, suspected to be secondary to disseminated intravascular coagulation due to surgical blood loss. However, she continued to have anemia and a persistently prolonged aPTT despite transfusion, prompting hematology consultation. A mixing study and measurement of factor activities demonstrated impaired coagulation and a Factor VIII activity of 2% (normal >50%) consistent with AHA. Recombinant porcine Factor VIII and prednisone were started. Simultaneously, the patient had a CT angiogram of the abdomen which showed active bleeding into the rectus sheath.
and a pelvic hematoma. She was transferred to the surgical ICU and interventional radiology
performed a bilateral uterine artery embolization.

The patient was monitored in the hospital for a total of 32 days during which she received
16 units of packed red blood cells, six units of fresh-frozen plasma and one unit of platelets. Her
Factor VIII levels did not improve despite fifteen days of prednisone, so cyclophosphamide was
added. Her Factor VIII levels rose to 20%. She received a total of 10 days of cyclophosphamide
and five months of prednisone. After stopping steroid treatment, her Factor VIII levels remain
normal, and she has had no evidence of recurrence of her AHA five years since her initial
diagnosis.

Case 2

A 48-year-old G3P1021 with a history of an uncomplicated myomectomy and elevated
titers of cardiolipin antibodies on prophylactic anticoagulation. With an appropriate window
since last dose of heparin (12 hours), neuraxial anesthesia was provided for the primary delivery.
Immediate postpartum hemorrhage, suspected due to atony, required multiple uterotonics, a
Bakri uterine tamponade balloon and, ultimately, re-operation (under general anesthesia) with
placement of a B-lynch suture and coagulation of friable tissue in the vesico-uterine space. She
returned on post-operative day 8 after awakening in a pool of blood. Upon readmission, she
received uterotonics, tranexamic acid, a blood transfusion and underwent an exploratory
laparotomy with supracervical hysterectomy due to ongoing uterine atony and bleeding.
Intraoperatively, oozing was noted from the surgical bed as well and skin edges. The patient was
transferred to the surgical ICU for postoperative management given massive hemorrhage and
concern for coagulopathy.
Twelve hours later, she had severe abdominal pain and a drop in hemoglobin concerning for an intraabdominal bleed and was taken for a second exploratory laparotomy. Venous bleeding in the vesico-vaginal space was cauterized and fresh frozen plasma, platelets and packed red blood cells were administered. Postoperatively her hemoglobin continued to downtrend and increasing abdominal distension was noted. A CT angiogram demonstrated left epigastric arterial bleeding and an IR embolization was performed, complicated by recurrent femoral access site bleeding requiring compressive sutures.

Hematology was consulted for a prolonged aPTT value in the setting of ongoing bleeding. It was initially presumed that the aPTT was falsely elevated in the setting of a lupus anticoagulant as she already had cardiolipin antibodies. The mixing study demonstrated immediate correction but subsequent prolongation in the aPTT with incubation suggestive of a time-dependent coagulation factor inhibitor. Factor VIII assay showed <0.5% activity (normal >50%) and subsequent inhibitor assay was positive at 82.4 Bethesda units (BU) (Titers <5 BU = low responders, titers >10 BU = high responders), diagnostic of AHA. FEIBA (Factor Eight Inhibitor Bypassing Activity), tranexamic acid, and prednisone were started. In the setting of persistent arterial bleeding after removal of a radial arterial line, additional recombinant Factor VIIa was given. She was discharged on hospital day 18. In total, she received 24 units of packed red blood cells, 12 units fresh frozen plasma, two units of platelets, and one of cryoprecipitate.

One month after discharge, her Factor VIII levels remained undetectable, and cyclophosphamide was added. Five months after delivery, she remains on cyclophosphamide with no additional bleeding.

Discussion
AHA is a rare form of coagulopathy with an incidence of 1.5 per million per year. (2) Despite the overall rarity, up to 20% of cases of AHA in women are associated with pregnancy, and its incidence in pregnancy is one per 350,000 births. (3) However, less than 100 cases have been published, the majority being from two large European registries. (3,4) Most are diagnosed in the postpartum period, although it is likely some have autoantibodies circulating during the antepartum period. (4) Delayed diagnosis is common, with a median time to diagnosis from delivery of 89 days. Other presenting symptoms include subcutaneous, mucosal, or musculoskeletal bleeding. (5) Although both patients were of advanced maternal age and had pregnancies resulting from ART, more data are needed to determine whether these are risk factors for development of AHA.

AHA is characterized by autoantibodies directed against Factor VIII, a key component of the intrinsic coagulation pathway. This autoantibody inhibits the action of Factor VIII to a variable degree, leading to a wide range of symptoms from no noticeable bleeding to profound spontaneous bleeding. Pregnancy represents a precipitating event that can lead to the formation of autoantibodies. The first evidence of AHA is a prolonged aPTT. Although the aPTT can be prolonged by other common factors including use of heparin, presence of lupus anticoagulant, or even disseminated intravascular coagulation, a prolonged aPTT with unexplained bleeding should prompt further workup (Figure 1). First, a mixing study, in which the patient’s blood is mixed with normal plasma, will show a persistently prolonged aPTT, due to the presence of the autoantibody. Next, coagulation factor levels (e.g., Factor VIII, IX, XI and XII) will reveal a Factor VIII level less than 50% of normal. Finally, a Factor VIII antibody assay will show the titer of the antibody present, which may correlate with the severity of the condition. (5)
The risk of mortality with AHA is 20%, though substantially lower in patients diagnosed in the peripartum period.(3,4) Thus, as soon as AHA is suspected, hematology should be consulted. Multidisciplinary discussions between obstetrics, hematology, transfusion medicine, anesthesiology, critical care, and interventional radiology should be coordinated as appropriate. As each surgical or procedural intervention carries a high risk of hemorrhage, there should be careful deliberate multi-disciplinary considerations for managing further bleeding episodes. If possible, medical management or interventional radiology procedures may be preferred to minimize bleeding from surgical sites. As seen in both cases, pregnancy-associated AHA can present with mucosal, venous, and arterial bleeding that is refractory to usual first-line interventions.

Due to the ongoing risk of bleeding in the peripartum period, treatment should be rapidly initiated in patients whose presentations are suspicious for AHA. Treatment generally involves two components: replacement of depleted Factor VIII and reduction of the inhibitor via immunosuppression (Table 1). Tranexamic acid (TXA) can be used as an adjunct for acute bleeding, but other traditional hemostatic agents such as desmopressin have limited utility and should be avoided. Although the aPTT should begin to normalize once Factor VIII levels reach 30-50% of normal, response to treatment should be judged clinically. Failed initial therapy, defined as failure of inhibitor titer to decline, or Factor VIII level to rise in 3-5 weeks, should prompt consideration of second line therapies. Reasonable second-line options include calcineurin inhibitors (e.g., cyclophosphamide), rituximab, or a combination of immunosuppressive agents.(6,7)

The long-term prognosis for patients diagnosed with peripartum AHA is mixed. Mortality occurs in <5% and remission in >90% of cases. However, depending on the initial
immunosuppressive regimen, relapse occurs in approximately 12-18% of patients and long-term follow-up with a hematologist is recommended.(8) Cases of transplacental transmission of antibodies to Factor VIII, with neonatal hemorrhage, have been reported.(9) Neither of the neonates in these cases demonstrated any signs of abnormal bleeding.

In summary, this pair of cases demonstrates a rare but important consideration for recurrent or delayed postpartum hemorrhage. Any peripartum patient with persistent unexplained bleeding and a prolonged aPTT should be promptly evaluated for AHA. Including AHA on the differential in this clinical presentation is critical as 1) failure to quickly diagnose and initiate treatment can lead to significant morbidity, 2) AHA is unlikely to respond to traditional medical and surgical management of postpartum hemorrhage, as these do not resolve the underlying coagulopathy. These cases underscore that early initiation of multidisciplinary care is vital to the successful management of peripartum AHA.

References


Figure 1. Algorithm for diagnosis of acquired hemophilia A

Table 1. Treatment options for acquired hemophilia A

<table>
<thead>
<tr>
<th>Agent</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor Replacement</strong></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Recombinant porcine Factor VIII</td>
<td>-Easy to monitor</td>
</tr>
<tr>
<td></td>
<td>-May require higher doses or may be less</td>
</tr>
<tr>
<td></td>
<td>effective if autoantibody is cross</td>
</tr>
<tr>
<td></td>
<td>reactive with porcine Factor VIII</td>
</tr>
<tr>
<td>Anti-inhibitor coagulant complex</td>
<td>-More effective for high Factor VIII</td>
</tr>
<tr>
<td></td>
<td>inhibitor titers (&gt;10 BU)</td>
</tr>
<tr>
<td></td>
<td>-No lab value to monitor</td>
</tr>
<tr>
<td></td>
<td>-Potential risk of arterial and venous</td>
</tr>
<tr>
<td></td>
<td>clot</td>
</tr>
<tr>
<td>Recombinant Factor VII activated</td>
<td>-More effective for high Factor VIII</td>
</tr>
<tr>
<td></td>
<td>inhibitor titers (&gt;10 BU)</td>
</tr>
<tr>
<td></td>
<td>-No lab value to monitor</td>
</tr>
<tr>
<td></td>
<td>-Potential risk of arterial and venous</td>
</tr>
<tr>
<td></td>
<td>clot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Immunosuppression</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid</td>
<td>-May take three weeks or more to see</td>
</tr>
<tr>
<td></td>
<td>clinical benefit</td>
</tr>
<tr>
<td></td>
<td>-Typical adverse events associated with</td>
</tr>
<tr>
<td></td>
<td>steroids</td>
</tr>
<tr>
<td>Cyclophosphamide (+ corticosteroid)</td>
<td>-May have faster response than steroids</td>
</tr>
<tr>
<td></td>
<td>alone</td>
</tr>
<tr>
<td></td>
<td>-Highest rate of complete remission</td>
</tr>
<tr>
<td></td>
<td>-Needs monitoring for bone marrow</td>
</tr>
<tr>
<td></td>
<td>suppression</td>
</tr>
<tr>
<td></td>
<td>-Breastfeeding contraindicated</td>
</tr>
<tr>
<td>Rituximab (7) (+ corticosteroid)</td>
<td>-Fewer and less severe side effects</td>
</tr>
<tr>
<td></td>
<td>-Very few cases reported in the literature</td>
</tr>
<tr>
<td></td>
<td>-Acceptable for use while breastfeeding</td>
</tr>
</tbody>
</table>