

## INHERITED COAGULATION DISORDERS IN PREGNANCY

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### EXECUTIVE SUMMARY

- Inherited coagulation disorders place women at risk for obstetric hemorrhage.
- It is crucial to identify women with inherited coagulation disorders early in care and to plan in advance for supporting their safety at birth.
- Maternal-fetal medicine, hematology, and anesthesia consultation should be obtained well in advance to coordinate antepartum, intrapartum, and postpartum care for women with inherited coagulation disorders.

### BACKGROUND AND LITERATURE REVIEW

The coagulation process is a complex biochemical chain reaction involving several pathways and proteins. Genetic abnormalities in any of these proteins can lead to serious coagulation problems. Although relatively rare in pregnancy, such abnormalities can lead to maternal hemorrhage events during antepartum, birth or postpartum and can have deleterious effects on the mother's and baby's health. Identifying patients with inherited coagulation disorders and carefully planning their care is crucial for optimal outcomes. Although postpartum hemorrhage can occur in these patients, coagulation defects are sufficiently rare that routine screening in patients with postpartum hemorrhage will not identify a large number of these patients.<sup>1,2</sup> Though incidence is low, this is an important group of individuals to identify and prepare for.<sup>3-12</sup>

The most commonly identified coagulation disorders are von Willebrand Disease (Factor VIII platelet adhesion and coagulant deficiency), Hemophilia A (Factor VIII coagulant deficiency), Hemophilia B (Factor IX deficiency) and Hemophilia C (Factor XI deficiency). Basic knowledge of these disorders will help to better understand the management recommendations below. In addition, less common disorders such as Factor XIII deficiency, congenital fibrinogen deficiency, and dysfibrinogenemia, can be diagnosed and successfully managed in pregnancy.<sup>13-15</sup>

**von Willebrand Disease (vWD)** is the most common hereditary coagulation abnormality described in humans with a prevalence of 1% in the general population.<sup>3,16,17</sup> It occurs less frequently as an acquired disorder (acquired von Willebrand Syndrome) manifested by the presence of auto-antibodies. Von Willebrand Disease is caused by a deficiency of the plasma protein that controls platelet adhesion (VIII:vWF) and decreased activity of the protein that stabilizes blood coagulation (VIII:C). The disorder can cause mucous membrane and skin bleeding symptoms, bleeding with vaginal birth, surgical events or

other hemostatic challenges. Women of childbearing age may be disproportionately symptomatic compared with other age groups.

Several types of vWD have been described.<sup>18</sup> Type 1 individuals make up 60-80% of all vWD cases and have a quantitative defect (heterozygous for the defective gene) but may not have clearly impaired clotting function. Decreased levels of vWF are detected in these patients, (10-45% of normal, i.e. 10-45 IU). Most patients lead nearly normal lives without significant bleeding episodes. Patients may experience bleeding following surgery (including dental procedures), noticeable easy bruising, or menorrhagia (heavy menstrual bleeding). Type 2 vWD patients (20-30% of all vWD cases) have a qualitative defect and the tendency to bleed varies between individuals. Individuals with Types I and II are usually mildly affected by the disorder and pass the trait in an autosomal dominant fashion.

Type III vWD is the most severe form; it is autosomal recessive and severely affected individuals are homozygous for the defective gene. Patients have severe mucosal bleeding, no detectable vWF antigen, and may have sufficiently low factor VIII. They can have occasional hemarthroses (joint bleeding), as in cases of mild hemophilia. Most vWD is diagnosed in women with a positive family history or menorrhagia. Blood testing for vWF activity provides confirmation of diagnosis.

**Hemophilia A** (Factor VIII coagulant deficiency) is a blood clotting disorder caused by a mutation of the factor VIII gene, which leads to Factor VIII deficiency. Inheritance is X-linked recessive; hence, males are affected while females are carriers or very rarely display a mild phenotype. It is the most common hemophilia, occurring in 1 in 5000 males. Women can, on rare occasion, exhibit a homozygous state if both parents carry the disorder. More frequently, carriers show atypical performance of “Lyonization” of the X chromosome (random inactivation of the X chromosome). Usually women have 50% activity but if inactivation of the “normal” gene occurs in greater frequency, lower levels can be seen.<sup>19</sup> Of note, Factor VIII activity usually increases during pregnancy.<sup>20</sup>

**Hemophilia B** (Factor IX deficiency) is a blood clotting disorder caused by a mutation of the Factor IX gene, also carried on the X-chromosome. It is the least common form of hemophilia (sometimes called “Christmas Disease,” after the first afflicted patient), occurring in about 1:30,000 males and very rarely in females. Diagnosis can be made by measuring levels of IX activity in the blood, which does not usually change during pregnancy.

**Hemophilia C** (Factor XI deficiency) is a rare condition in the general population (less than 1:100,000) but more common in Ashkenazi Jewish patients, and it can occur in both males and females.<sup>7,21</sup> Up to 8% of these individuals are carriers (autosomal recessive) of the gene, which is located on Chromosome 4. Treatment is not usually necessary

because patients have approximately 20-60% factor XI activity; however, they should be followed closely since the postpartum hemorrhage rate is 20%.

**Rarer Disorders** Congenital Factor XIII deficiency is a rare autosomal recessive disorder who when identified can be successfully followed and treated in pregnancy with replacement factor.<sup>13</sup> Patients with congenital fibrinogen deficiency will require monitoring of levels and replacement with targets of > 0.5-1.0 g/L in the antepartum, intrapartum and postpartum periods.<sup>14</sup> Inherited dysfibrinogenemia requires similar replacement of fibrinogen to maintain levels > 100 mg/dl and in addition should be given anticoagulation.<sup>15</sup>

**Diagnosis in pregnancy** of any of these coagulation disorders may be difficult due to the variability of clotting factor activity caused by hormonal changes of pregnancy.<sup>22</sup> When a patient with an inherited coagulation disorder delivers, one must be concerned about extra-uterine bleeding and hematomas and the effect of the disorder on the fetus. Cesarean section is rarely recommended.<sup>4,5,23</sup> Autoimmune acquisition of these disorders has been described and therefore may occur despite the lack of familial history.

## RECOMMENDATIONS

1. Review family, surgical and pregnancy history for possible clinical symptoms of excessive bleeding following surgery (including dental procedures), noticeable easy bruising, joint hemorrhage or menorrhagia (heavy menstrual bleeding).
2. Request the following laboratory screening tests for patients with suspected disorders<sup>18,19</sup>:
  - von Willebrand Disorder: Measurement of Ristocetin Co-Factor Activity and von Willebrand Antigen (VIII:Ag) activity
  - Hemophilia A: Measurement of Factor VIII activity (Factor VIII:C assay)
  - Hemophilia B: Measurement of Factor IX activity (If Factor VIII:C is normal)
  - Hemophilia C: Measurement of Factor XI activity

Other tests performed for patients with bleeding problems: complete blood count (especially platelet counts), APTT (activated partial thromboplastin time), prothrombin time, thrombin time and fibrinogen level. Note that patients with von Willebrand disease typically display normal prothrombin time and variable prolongation of partial thromboplastin.

3. Affected patients or carriers, or patients with suspected history should consult with a hematologist who has specific interest and knowledge of coagulation disorders.<sup>4,5</sup>

4. Obtain perinatal and anesthesia consultation for planning and coordination of antepartum and intrapartum management.<sup>4,5</sup> In general regional anesthesia must be given with caution given the risks of spinal hematoma. Route of delivery for most patients with carrier status which may cause neonatal coagulation disorders, e.g. Factor VIII deficiency, should still be reserved for obstetrical indications since studies have not shown a protective effect of cesarean section.<sup>4,5</sup> Individualized decisions should be made in a multidisciplinary fashion.
5. Refer patients for genetic counseling regarding possible testing and evaluation of the fetus and newborn.<sup>4,5,23</sup>
6. Develop intrapartum and postpartum management plans well in advance of the anticipated date of birth so specific medications and blood components are available at the time of delivery and given in consultation with a hematologist<sup>4,5</sup>
  - von Willebrand Disorder: Mild forms can be treated with desmopressin acetate (DDAVP) but more severe forms require vWF and VIII factor replacement.<sup>12</sup> DDAVP challenge testing can identify whether patients will respond to this medication.
  - Hemophilia A/B: Concentrates of clotting factor VIII (for Hemophilia A) or clotting factor IX (for Hemophilia B) are slowly dripped in or injected into a vein. Consider DDAVP adjunctive therapy.
  - Hemophilia C: FFP is the first product used to treat patients with hemophilia C. The main advantage of FFP is its availability. Disadvantages of its use include the large volumes required, the potential for transmission of infective agents and the possibility of allergic reactions.
  - Factor XI activity: Factor XI concentrates provide the best source for factor XI replacement.

## EVIDENCE GRADING

**Level of Evidence: III C.** Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. Recommendations based primarily on consensus and expert opinion.

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