Editorial

Inherited Bleeding Disorders in Females

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Inherited bleeding disorders among women are often unrecognized or misdiagnosed.[1] About 10 to 20% of women manifesting menorrhagia are believed to have an underlying inherited bleeding disorder.[2] During pregnancy there are greater risks of miscarriage and bleeding complications. At the time of childbirth, women with bleeding disorders experience postpartum haemorrhage (PPH), particularly delayed or secondary PPH. Vaginal or vulvar haematomas, extremely rare in women without bleeding disorder, are not uncommon. Further, there is an increased risk of developing haemorrhagic ovarian cysts and possibly endometriosis.

The commonest inherited bleeding disorder in females is von Willebrand Disease (vWD), followed by platelet function defects and some autosomal recessive coagulation factor deficiencies. Rarely female carriers of haemophilia can also have obstetric or gynaecologic complications.[3]

von Willebrand Disease (vWD) is a common inherited bleeding disorder with an estimated prevalence of 2% of the population. Bleeding in vWD is mainly mucocutaneous. The most common symptoms are easy bruising, frequent or prolonged nose bleeds, heavy or prolonged menstrual bleeding (menorrhagia) and prolonged bleeding following injury, surgery, dental work and child birth. Gastrointestinal bleeding can also occur. However, unlike haemophilias, bleeding in the joints is rare.

Most **Platelet Function Disorders** clinically mimic the features of vWD with prolonged muco-cutaneous bleeding. Platelet membrane receptor deficiencies result in the rare, but well characterized syndromes of defective clot initiation such as Bernard–Soulier Syndrome.[4] Platelet storage pool defects are the disorders affecting the extension phase of clot formation. Glanzmann thrombasthenia, with qualitative or quantitative disturbance in the platelet membrane GP-IIb/IIIa complex is the prototypic defect of the cohesion/ aggregation phase of microthrombi formation. Many of these disorders share common treatment modalities.

Diagnosis of vWD is difficult. There is no single definitive test that confirms the diagnosis. Prolonged bleeding time & APTT and normal PT, with aggregation studies showing aggregation with all agonists except Ristocetin can establish the diagnosis of vWD. vWD and Bernard Soulier Syndrome give similar results on platelet aggregation studies, but in vWD patient's plasma plus control plasma will give normal aggregation with Ristocetin. In Bernard Soulier Syndrome there is thrombocytopenia with giant platelets on peripheral smear. Ristocetin cofactor assay and vWF antigen levels, which estimate vWF functions and levels respectively, along with Factor VIII levels are required to specifically establish the diagnosis of vWD.

In Glanzmann's thrombasthenia there is severely impaired aggregation with high concentrations of ADP, collagen and arachidonic acid but normal aggregation with ristocetin, while reverse hold true for Bernard Soulier Syndrome.[5,6]

Haemophilia in females: The inheritance of haemophilia A and B (Factor VIII and factor IX deficiency) is X-linked recessive. The mechanism by which haemophilia may occur in females include extreme lyonization, non–random X chromosome inactivation, X hemizygosity as in 45XO, Turner syndrome, and double heterozygosity occurring in daughters of haemophilic father and carrier mother.

Autosomal Recessive Congenital Bleeding Defects in Females: Unlike Haemophilia A and B, deficiencies of all the other plasma clotting proteins such as afibrinogenemia, hypofibrinogenemia, deficiencies of factor V and combined factor V and VIII, VII, X, XI and XIII are inherited in an autosomal recessive manner, meaning they can affect both males and females.

Prolongation of PT indicates a deficiency of extrinsic pathway, while prolongation of APTT indicates a deficiency in the intrinsic pathway. Prolongation of both PT and APTT suggests a defect in the common pathways, including deficiency of factor X, V, II or I or acquired disorders, e.g., vitamin K deficiency or liver

disease. Further, mixing studies along with factor assays can establish the diagnosis.

Clinical evaluation of a female suspected of having an underlying bleeding disorder should include a history, physical examination, laboratory screening tests along with keeping in view all the possible causes which can lead to this type of bleeding. Symptoms like epistaxis lasting for more than 10 minutes, spontaneous bleed, prolonged bleeding after dental work or post operative bleed are highly suggestive of a bleeding disorder.

General Approach to Management: The first step in treatment and prevention of bleeding is education of the patient and the family. All must be counselled that mucocutaneous bleeding will be common. Serious haemorrhage can occur in the event of trauma, surgery, in the gastrointestinal tract and frequently with menses or the postpartum period.[7]

Hormone Therapy: Hormonal therapy (oral contraceptives, depot medroxyprogesterone acetate, danazol, GuRH analogs) represent the first line treatment. Oral contraceptives are very effective in raising the levels of all clotting factors except factor IX. These agents can manage heavy menstrual and other bleeds. In patients with qualitative vWF defects, oral contraceptives are not as effective, since the hormones raise the level of vWF but do not correct the inherent structural defect. For these women, oral contraceptives will probably still be of some benefit, but other therapies may also be necessary. It seems preferable to avoid combined oral contraceptives at menarche or in young girls if they respond to antifibrinolytics, such as oral tranexamic acid (15-25 mg/kg body weight) given 3 times a day for 4 to 5 days. For bleeding that is not responsive to oral contraceptives, the use of pure progestational agents can be very helpful. These will cause a thickening of the uterine lining (a secretary endomterium) and stop the bleeding.

Platelet Transfusions: Significant bleeding or surgical procedures may require platelet transfusions. In patients with inherited platelet defects repeated and inappropriate platelet transfusions from multidonor source predispose to the development of antiplatelet antibodies resulting in a variable degree of platelet refractoriness. The treatment described includes antibody removal by plasmapheresis, transfusion of single donor and HLA matched platelets, and infusion of gamma globulins or rFVIIa.

Desmopressin Acetate (DDAVP) is available in the injectable form (intravenous or subcutaneous) and a high potency intranasal spray.[8] It is chemically related to vasopressin and causes a rapid rise in circulating plasma levels of factor VIII and vWF by stimulating their release from lining of blood vessels. Over 90% patients respond to DDAVP at a dose of 0.3 ug per kilogram by intravenous infusion over 30 minutes, and although effective for mucosal bleeding, DDAVP may not reduce menorrhagia. The intranasal form of DDAVP, given at 150 ug or 1 ml of 1.5 mg/ml solution, one puff in one nostril, for those less than 50 kg in weight, and one puff in each nostril for those more than 50 kg in weight, may also reduce menorrhagia when given as an adjunct to hormonal therapy.

Fresh Frozen Plasma (FFP) and Cryoprecipitate: For women who are not responsive to DDAVP or aggressive hormone therapy, replacement of the deficient or defective clotting protein becomes necessary. The ideal is to administer virally attenuated concentrates. But, if factor concentrates are not available, plasma products can be used. Each unit of FFP contains approximately 200 IU of all clotting factors, while cryoprecipitate contains vWF, F VIII, F XIII and Fibrinogen.

Factor Concentrates: Haemostatically active factor concentrates are now available for deficiencies or defects of factor II, VII, VIII, IX, X and vWF. The most widely used products for vWD are Humate P or Haemate P and Alphamate SD or Koate.

Antifibrinolytics: Medications such as tranexamic acid and aminocaproic acid can be of value in managing heavy menstrual as well as mucous membrane bleedings in nose and mouth, but not for joint and renal bleeds. These medications rather than assisting in clot formation, keep the clot in place longer once it has formed by breaking the enzymes responsible for fibrinolysis. Tranexamic Acid is the first line medicine in different bleeding episodes; it is given in a dose of 10mg/kg, intravenously or 15 mg /kg per oral. Local application of injection is also useful.

Iron supplementation: Iron supplementation is of paramount importance in all cases and there is likelihood that these cases may require iron for extended periods.

Non-Steroidal Anti Inflammatory (NSAID): Most NSAIDs hamper platelet adhesion and aggregation. However, some drugs, like choline-magnesium trisalicylate, salsalate and cox-2 inhibitors do not interfere with platelet functions, hence can be a viable option to control pain associated with ovulation and menstruation.

Recombinant Factor VII (rFVIIa)[9] binds to tissue factor (TF) expressed on the damaged vascular bed. This TF-F VIIa complex activates F-IX and F-X on TF bearing cells. On the surface of activated platelets, F VIIIa and F IXa gather to activate large quantities of FX, which eventually result in large thrombin burst enabling the conversion of fibrinogen into fibrin with initial clot formation. Exogenous administration of rFVIIa accelerates this process and helps in securing haemostasis by clot formation. The recommended dose

of recombinant factor VIIa is between 19-120 ug/kg body weight, intravenously, over a time of 2 to 3 minutes. The response is usually seen after half an hour. Limitations to use of rFVIIa are its short half life (2 hours) and high cost. It is contraindicated in disseminated intravascular coagulation.

Management during Pregnancy: Vacuum extractions, forceps, fetal scalp electrodes and fetal scalp blood sampling should be avoided if the fetus is known or thought to be at risk for a congenital bleeding disorder, for a high risk of cephalohaematoma or intracranial bleeding. A caesarean section should be performed for obstetrical indications only. Epidural and spinal anaesthesias are contraindicated if there is coagulation defect. There is no contraindication to regional anaesthesia if coagulation is normalized. The risk of early and late post-partum haemorrhage is increased in women with inherited bleeding disorders. Intramuscular injections, surgery and circumcision should be avoided in neonates at risk for a severe hereditary bleeding disorder until adequate work up and preparation are exercised.

The levels of factor VIII and vWF rise during normal pregnancy. The rise is particularly marked during the third trimester.[10] The baseline level of factor VIII needs to be checked early in the pregnancy, and again at some stage in the last trimester at around 36 weeks.

If treatment is required in carriers of either haemophilia A or B during pregnancy, then recombinant (genetically engineered) products should be regarded as products of choice. DDAVP can also potentially boost the plasma level; of vWF and factor VIII. But it has no effect on factor IX level; hence it is of no value in carriers of haemophilia B.

With regard to haemophilia, an ultrasound examination during pregnancy to determine fetal sex is strongly recommended. This may influence decision in the management of the actual delivery. If the fetus is female it will not have a very low factor VIII level.

In vWD the levels of vWF usually rise to within normal range by the third trimester and haemostatic support is rarely required. But the low levels in first and second trimesters make miscarriage a possibility. DDAVP is effective in type 1 vWD. Women with vWD can have a normal vaginal delivery and epidural anaesthesia if their factor VIII level (often used as a surrogate marker for vWD) is more than 40 IU/dl and a caesarean section if their factor VIII level is greater than 50 IU/dl. Post partum haemorrhage, more often in type-2 vWD than type-1 vWD, is an important complication, and needs comprehensive management. Type III vWD requires factor support to increase F VIII level to about 50 IU/dl peripartum and for 1 to 2 days post-delivery.

In most of the women with inherited bleeding disorders pregnancy maintenance is usually a big issue, and with good management these females can have successful outcome. In females with inherited platelet defects caesarean section, supported by single-donor platelet transfusions in pre- and postpartum period, is safely applicable with no adverse events.

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