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Reproductive Life of Women with Inherited Bleeding Disorders

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Women with inherited bleeding disorders (IBD) naturally aspire to have a safe reproductive life, just like other women. However, compared to men with IBD, women face additional challenges related to reproductive health, such as complications with menstruation, pregnancy, and childbirth.[1] Fortunately, management options for women with IBD have expanded due to improved diagnostic facilities, support from hemophilia treatment centers (HTC), and increased awareness of these disorders. Over time, more treatment options have become available. Advances in molecular technology and prenatal diagnostic techniques (PND), along with assisted reproductive technologies like Pre-Implantation Embryo Selection (PIES) in conjunction with In Vitro Fertilization (IVF), have also provided new avenues of hope.[2,3]

Von Willebrand Disease (VWD), autosomal recessive bleeding disorders, platelet function defects, hemophilia carriers, and others make up the predominant group of females with inherited bleeding disorders (IBD). Although hemophilia in women is rare, it can occur. In our region, the prevalence of autosomal recessive inherited bleeding disorders is higher than in the Western world due to consanguineous marriages.[4]

Menorrhagia at menarche is a common complaint among this cohort. Pregnancy and childbirth also pose significant challenges, with risks of recurrent miscarriages, and bleeding during pregnancy, delivery, and the postpartum period. Postpartum hemorrhage (PPH) is frequent in women with all types of bleeding disorders if replacement therapy is not administered for several days after delivery.

Inherited bleeding disorders can significantly affect a woman's quality of life by limiting activities, work, family, and social interactions, as well as altering their reproductive health.[5] Normally, pregnancy is associated with increased levels of fibrinogen, Factor VII (F-VII), Factor VIII (F-VIII), Factor X (FX), and von Willebrand factor (VWF), especially in the third trimester. Factors II (F-II), V (F-V), IX (F-IX), and XIII (F-XIII) remain relatively unchanged during pregnancy. These changes contribute to the hypercoagulable state of pregnancy and, in women with inherited bleeding disorders, help improve hemostasis. However, women with coagulation deficiencies do not reach the same factor levels as other women, and hemostatic abnormalities often persist, particularly in severe cases.[6]

Maintaining vigilant follow-up throughout pregnancy and ensuring a successful delivery while managing postpartum complications is akin to walking a tightrope.[7]

During pregnancy, the levels of VWF factor start to increase early in the first trimester and continue to rise progressively with advancing gestational age. Factor levels are shown to peak in the few hours postpartum. Thereafter levels of VWF fall rapidly, approaching baseline at around one week postpartum and returning to baseline non-pregnant values within a few weeks.[8]

However, this is not the case in patients with qualitative or more severe VWF deficiency. The rise in dysfunctional VWF, during pregnancy, may exacerbate the thrombocytopenia and bleeding tendency in women with type 2B. In type 2B VWD and in cases with thrombocytopenia it is required to maintain the platelet count greater than 50 X 10^{9}/l.[9] Active management, especially of third trimester, is recommended. Invasive monitoring procedures, mid cavity rotational forceps best to be avoided. [10] Some factors, like factor XI are a challenge in pregnancy due to poor correlation

between factor levels and bleeding tendency. No specific treatment for F-XI deficiency is required antenatally, unless there is a planned invasive procedure or for bleeding after a miscarriage.[11]

The haemostatic defects in women with platelet function disorders and severe clotting factor deficiencies, such as type 3 VWD also remained unchanged in pregnancy. Therefore, it is important to assess haemostatic profile during the third trimester, in order to create an individualized management plan for each woman.

Haemophilia carriers is a mentionable group in women with IBD. Haemophilia A carriers, experience rise in F-VIII:c level during pregnancy, while carriers of haemophilia B have no similar benefit.[12] Carriers of haemophilia B may therefore need treatment with factor IX concentrates for delivery. Awareness of haemophilia carrier status before pregnancy is advantageous. It gives time to cope with the diagnosis, access information about reproductive options, and proper genetic counseling. Further complex decisions with prenatal diagnosis (PND) or preimplantation genetic diagnosis (PGD) in families affected by the most severe form of haemophilia.[13,14] Receiving a diagnosis of carrier ship is never easy. It can imply psychological issues which need to be anticipated.[15-17]

To effectively manage delivery, factor levels should be assessed at 28 and again at 32 or 34 weeks of pregnancy. After birth, Factor VIII (F-VIII) levels progressively return to their baseline within a few days or weeks, which can increase the risk of postpartum hemorrhage (PPH). Hemophilia carriers have a reported probability of 19% for primary PPH and 2% for secondary PPH. Treatment with DDAVP or factor concentrates in the early postpartum period may be necessary due to the post-delivery decline in F-VIII levels.

Bleeding episodes during pregnancy are uncommon in hemophilia carriers, thus the need for replacement therapy is generally limited. Additionally, the miscarriage rate among pregnant hemophilia carriers has not been reported to be elevated.[18,19]

In perinatal management it is vital to have a written multidisciplinary plan, with obstetrician, anesthetist, pediatrician and haemophilia treatment centre (HTC) on board. delivery in a specialist maternity unit helps to limit both maternal and fetal bleeding risk. The mode of delivery should be decided. Feasibility of obtaining factor concentrates should be anticipated. The type of product to be used for neonate, in case of bleeding, should be discussed and decided with parents.[10] It is required to maintain factor levels above 50 IU/ml cover for about three days in case of vaginal delivery and five days in case of cesarean section is recommended. Monitoring of haemoglobin levels and coagulation parameters during post-partum period may help to assess the need to further treatment. The potential of antifibrinolytics (e.g.,Transamine) in reducing the risk of PPH needs to be properly defined.[20,21]

If a female with IBD opted to conceive then hormonal therapies (Levonogestreil IUD, combined oral contraceptives, progestrins, GNRH therapy with add-back therapy, etc) need to be restrained and there will be careful adoption of haemostatic measures (tranexamic acid, epsilon amniocorporic acid, DDAVP ,etc). It is recommended to check factor levels at booking, in the third trimester and prior to invasive procedures .[22-24]

Factors such as personal and family bleeding history also need to be taken into account, especially for disorders with an unpredictable bleeding tendency such as F-VII and F-IX deficiency. Women with mild VWD and carrier of haemphilia A usually do not require prophylaxis during labour because of the pregnancy induced rise in F-VIII and VWF levels. However, carriers of haemophilia B and women with F XI deficiency and other severe rare bleeding disorders are likely to require prophylactic treatment because their bleeding defects usually persist during pregnancy. [25]

Different modes of delivery carry different risks for the mother and the newborn. It has been found that incidence of extra-cranial and intra-cranial haemorrhage is lowest in planned cesarean section deliveries.[26] Where abnormal fetal haemostasis is possible, traumatic delivery should be avoided, including prolonged labour or the use of ventouse section, rotational forceps or invasive fetal monitoring. [27] Cesarean section is associated with more maternal morbidity and may present haemosatic challenges for the mother. Guidelines do not consistently recommend cesarean section over vaginal delivery.[28]

In order to avoid bleeding complications appropriate treatment should be provided before CVS, aminocentesis, invasive procedures for PND, preimplantation genetic diagnosis (PGD) and

termination of pregnancy. Invasive procedures can be safely performed during pregnancy if factor levels are within agreeable limits.[10] Prophylactic treatment is required for those with low factor levels, bleeding phenotype and previous history of PPH.[2] Where indicated, Recombinant F-VIIa, because of it's short life (2 hours) can be given in late established labour and a repeat dose may be required, depending on how labour progresses.[29]

It is safe to site a regional block in women with IBD provided the coagulation defect has returned to normal during pregnancy, or has been corrected with prophylactic treatment. Use of regional block anaesthesia is contraindicated in women with severe or un-predictive disease Better to avoid spinal or epidural anaesthesia because of risk of haematoma formation. Signs and symptoms of spinal haematoma are inconsistent but include acute onset of redicular back pain, bladder dysfunction and sensory and motor deficits. For cesarean sections the alternative is general anaesthesia and the potential risk of spinal haematoma must be weighed against the risks of general anesthesia, especially in at risk patients such as those who are in labour and have a full stomach. These risks include hypoxemia associated with difficulties maintaining the airway, pulmonary aspiration, and thromboembolic complications.[30,31]

Central neuraxial bock best to be avoided, unless adequate replacement therapy has been conformed in women with type -2 and type-3 VWD, severe homozygous rare bleeding disorders, severe platelet function defects , F-XI deficiency with clinical bleeding phenotype, and type 1 VWD or carriers of haemophilia with third trimester levels less than 50 IU.dl.[10] A single-shot spinal anesthesia is a safer option than an epidural in some situations and removes the potential risk of vessel damage from an epidural catheter. The reduction in anaesthetic related maternal mortality over the last decades is associated with an increase in use of regional anaesthesia for caesarean sections alongside an increased awareness of the important issues and better organization and resources of obstetric services

Although regional techniques are the preferred methods for providing anaesthesia for cesarean section, there are circumstances when general anaesthesia is indicated. These include emergency procedures for which there is insufficient time to establish regional blockade, inadequate or failed regional anaesthesia, and an uncorrected maternal bleeding diathesis for which an epidural is contraindicated.[30,31] There is an agreement that all vaginal deliveries should avoid instrument associated delivery (forceps and vacuum), as well as fetal scalp monitoring and fetal scalp blood sampling .Vacuum extraction and high forceps seem to lead to the highest incidence of ICH and EXH, with low forceps and unassisted vaginal delivery being the least possible.[5]

Despite the critical role of uterine contractility in controlling early postpartum blood loss, women with bleeding disorders are at an increased risk of PPH. Primary PPH up to 24 hours after delivery and secondary PPH24 hours to 6 weeks after delivery Delayed PPH, is rare in general population with a frequency of less than 1%. In contrast, women with bleeding disorders are particularly vulnerable to this type of bleeding. Coagulation factors, which are elevated during pregnancy return to baseline within 14-21 days. That translates into increased incidence of secondary PPH in women with inherited bleeding disorders.[32,33] A number of factors including maternal age, pre-pregnancy factor levels, bleeding score and a family history of bleeding may be important determinants of PPH in women with IBD.[34,35]

Miscarriages are more common in women with deficiency of F-XIII and Fibrinogen (afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia). Fibrinogen and F-XIII play an important role in placental implantation and maintenance of pregnancy through a complex interaction that involves F-XIIIa, which cross links fibrinogen and fibronectin at the sites of implantation. Thus, deficiency of F-XIIIa and fibrinogen may result in detachment of placenta from uterus and subsequent miscarriage.[37]

In some women thrombocytopenia is discovered for the first time in pregnancy. In these cases, it is difficult to differentiate from acquired thrombocytopenia. In women with Inherited platelet defects (IPD), pregnancy is generally uncomplicated but bleeding risks from invasive procedures must be managed carefully. Delivery should be planned in a tertiary centre due to bleeding risk in mother and baby. Risk of postpartum haemorrhage is predicted by the type of IPD(with Glanzmann's thrombasthenia having a particularly high risk), pre-pregnancy bleeding score , a history of excess bleeding after past surgeries, or a platelet count of less than 80 X 10^9 /l at time of delivery. Neonate born

to a parent with a platelets function disorder is not usually at risk of bleeding due to the autosomal recessive nature of the most platelet function disorders.[38,39]

The neonate should be considered at risk for hemophilia until factor level results confirm or rule out the diagnosis. Cord blood factor levels and activated partial thromboplastin time (APTT) should be assessed. Cranial imaging may be required based on obstetric circumstances or the risk of brain hemorrhage.[40] Newborns may present with bleeding complications, especially those who have inherited platelet disorders or are affected by the transplacental passage of maternal antiplatelet antibodies, or intracranial bleeding during delivery—both of which can be fatal. Mothers with Glanzmann's thrombasthenia are particularly at risk of developing (or having preformed) antiplatelet antibodies, which cross the placenta and inhibit fetal and neonatal platelet function. This occurs because their offspring will usually be heterozygous for this disorder and therefore express the platelet antigens missing on the mother's platelets.[27]

Fortunately, most congenital bleeding disorders do not place the newborn at a significantly increased risk of bleeding. However, severe subtypes can present with life-threatening bleeding at birth. It is crucial for clinicians to suspect congenital bleeding disorders in any neonate with unexpected or abnormal bleeding, even in the absence of a family history.[28] The clinical presentation of congenital bleeding disorders in neonates differs from that in older children or adults. A congenital bleeding disorder should be suspected in a neonate with extracranial hemorrhage (e.g., cephalohematoma, subgluteal hematoma), intracranial hemorrhage, bleeding from delivery trauma (e.g., forceps or vacuum use), mucocutaneous bleeding (e.g., petechiae, purpura), post-circumcision bleeding, or bleeding from the umbilicus. Musculoskeletal bleeding (e.g., joint or muscle bleeding) and epistaxis, which are common in older children with bleeding disorders, are rare in neonates.[28]

Parents may choose to make an informed decision about continuing or terminating an affected pregnancy. A multidisciplinary approach for delivery in a tertiary care center should be planned if the fetal status is unknown or if the neonate is confirmed to have hemophilia after prenatal diagnosis (PND). Women with inherited bleeding disorders can pass the gene defect to their offspring, placing them at risk of having an affected child, depending on the inheritance pattern of the disorder. The decision regarding reproduction is fundamentally complex and challenging. Proper genetic counseling, with a thorough discussion of all aspects, is essential. Advances in molecular genetics and technology have created new opportunities, expanding reproductive options for these women.[3]

Non-invasive PND of haemophilia by microfluidics digital PCR analysis of maternal plasma DNA has been performed in a limited number of centers and may limit the request for chorionic villous sampling (CVS) in future.[36] The option of prenatal diagnosis (PND) varies in different set ups. Prenatal diagnosis of inherited bleeding disorders entails non-invasive and/or invasive tests. Invasive procedures include chorionic villous sampling (CVS), aminocentasis and fetal cord blood sampling (cordocentasis), whereas non-invasive tests are mainly used for diagnosis of fetal gender in case of haemophilia through ultrasound examination Some countries propose access to PND only in cases of severe haemophilia in affected male relatives , others may extend this option to moderate or even mild haemophilia. Uptake of the option for termination of pregnancy is left to the choice of couple. Advances in the treatment of patients with severe haemophilia, including improved prophylactic regimens, non-replacement therapies and gene therapies, may influence parental choices. The sequence for PND includes a fetal sex determination from nine gestational weeks, leading to chorionic villous sampling and gene analysis (11-14 gestational week) in case of male fetus.[40,41]

Prenatal diagnosis is an option when a family is known to be at risk of having a child affected with a specific bleeding disorders. For example this can occur when a woman is a known/suspected hemophilia carrier and as such, has a 50% chance of having an affected son (if she is carrying a male fetus) or when a couple are known to be carriers of recessive mutations of coagulation proteins (e.g., factor VII,X or XII) and as such have a 25% chance of having an affected child . In the former setting it is critical to determine the fetal sex as, in general female newborn carriers are at a significantly lower risk of suffering from bleeding a neonates as in comparison to newborn males with haemophilia.[28] If parents are not planning termination of the affected fetus, then the value of prenatal testing

may or may not be justifiable to many parents given the risks of prenatal testing .For such families, it is best to assume that the fetus is affected and plan the labour and delivery accordingly. [28]

Preimplantation Genetic Diagnosis (PGD), followed by Pre-Implantation-Embryo Selection (PIES) in conjunction with In-vitro Fertilization (IVF) is an upcoming reproductive technique available for couples at risk for having a child with certain genetic disorder. In this technique embryos created in-vitro are analyzed for the specific genetic abnormality and only unaffected embryos are transferred to the uterus. This can prevent the birth of an affected child and obviates the need for prenatal diagnosis (PND). [42] PGFD is likely to become a realistic option for more couples at risk of having child affected by haemophilia or other severe inherited bleeding disorders in near future. PGD requires the female partner to undergo an in-vitro fertilization cycle, and the eggs or embryos are then biopsied. [43,44]

It is encouraging to witness the efforts, put in by haematologists, to help the women with inherited bleeding disorders, more so in their reproductive issues. Access to proper management through treatment centers (HTC) enables them to have a better quality of life which can lead to accomplishment of a fruitful reproductive outcome. [45]

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