[haematologica reports]
2005;1(10):43-46

# Congenital bleeding disorders and pregnancy

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A B S T R A C T

Congenital bleeding disorders are not so infrequent and they can increase frequency and severity of bleeding complications during and after pregnancy. Bleeding history, such as presence of menorrhagia, methrorrhagia, peritoneal haemorrhage at ovulation, bleeding after miscarriage or abortion or following childbirth, can identify patients with congenital bleeding disorders and anticipate possible complications during pregnancy: the most common congenital deficiencies of clotting factors are von Willebrand disease and haemophilia A and B carrier status. Complications are also reported for other rarer coagulopathies, including platelet disorders. The management and the prophylaxis of bleeding in pregnant women depend on the type of hemostatic defects and it is based on replacement therapy with the deficient clotting factor concentrate. Desmopressin, platelet transfusion and tranexamic acid are other useful weapons in particular occasions and diseases. Other general measures are to avoid forceps and vacuum extraction, to perform a Caesarean section for obstetrical indications only, to allow epidural and spinal anaesthesia only when haemostatic clotting factor levels can be warranted, and to consider the risk of primary and secondary postpartum haemorrhages. In conclusion, pregnancy in women with inherited bleeding disorders is at risk for complications and it requires a multidisciplinary approach involving consultants in obstetrics, anaesthesiology, haematology, and paediatrics.

Key words: haemophilia carriers, von Willebrand disease, pregnancy, rare bleeding defects, bleeding complications

Bleeding problems among women are often unrecognized or misdiagnosed in the general population and very little information is available about frequency of gynaecological bleeding complications (menorrhagia and post-partum bleeding). Congenital bleeding disorders in women can increase frequency and severity of gynaecological bleeding complications.[1-8]

This paper will illustrate epidemiology of congenital bleeding disorders in women, clinical manifestations during pregnancy and delivery and treatment modalities.

## Epidemiology

Congenital bleeding disorders are not as rare as it is generally considered.[9,10]

Haemophilia A and B affect one person out of 10,000 inhabitants.[10] The gene defect, inherited as an X-linked disorder, leads to a qualitative and quantitative plasma factor VIII deficiency in males that predisposes to recurrent joint and muscle bleeds and mucosal bleeds, and, not infrequently, intracranial and intraperitoneal haemorrhages can occur. Bleeding frequency is directly proportional to the FVIII plasma levels, being more severe with levels less than 1% of normal. The spontaneous bleeding tendency starts in the first years of age and its recurrence in joints causes a progressive impairment of joint function with severe and long-lasting crippling arthropathy.[11] A significant proportion of female carriers of haemophilia, who can be considered to be at least as frequent as the patients with haemophilia, have a reduction in levels of factor VIII (or IX).

The baseline level is seldom lower than 20% of the normal level and should therefore be enough to protect against significant bleeding problems in day-today life. However, female carriers with these low levels of factor VIII or IX are at risk of excessive bleeding from surgery or other invasive procedures. Women with clinical haemophilia A or B due to extreme lyonization or double heterozygosity in daughters of haemophilic fathers and carrier mothers are very rare.

Von Willebrand disease (VWD) is the most

frequent congenital bleeding disorder[12] and is caused by: quantitative (type 1 and 3 VWD) or qualitative (type 2 VWD) defects of von Willebrand factor (vWF), a protein encoded on chromosome 12 and synthesised in endothelial cells. VWD is inherited as an autosomal dominant condition, and thus either sex may inherit the condition. Some reports report a prevalence of 1 patient out of 100 inhabitants. VWF is essential for platelet adhesion to endothelial cells and to protect factor VIII from degradation and uptake into endothelial cells. VWD typically results in mucocutaneous bleeding, such as easy bruising, prolonged bleeding from cuts and scratches, epistaxis, and menorrhagia.[12]

Women with other congenital hemostasis defects may be more rarely encountered: each of them have a frequency ranging from 1 out of 500,000 (FVII deficiency) to 1 out of 2,000,000 inhabitants (FXIII deficiency).[13]

Afibrinogenaemia is caused by the deficiency of fibrinogen (factor I), a protein encoded on chromosome 4 and synthesised in hepatocytes. Fibrinogen, which is also essential for platelets aggregation, may be associated with menorrhagia, recurrent miscarriages, and postpartum haemorrhage.[1,2,13]

Deficiency of factor XI, a serine protease encoded on chromosome 4, is associated with a bleeding tendency particularly with levels of less than 15%, even though post-operative bleeding can occur with much higher levels.[1] Factor XI deficiency is common in Ashkenazi Jews and other ethnic groups. Menorrhagia is a frequent manifestation in women with factor XI deficiency reported by about half of them.[14,15] Because of the unpredictable bleeding predisposition, peri-partum period can be at risk for bleeding complications.[3, 5]

Factor XIII deficiency is very rare, but is associated with a very serious bleeding tendency as well as poor wound healing. Some reports suggested that women with FXIII deficiency are prone to infertility and/or recurrent miscarriages.[6] Other congenital clotting disorders, such as factor X, factor VII, factor V, prothrombin deficiencies and platelet disorders, are transmitted as autosomic recessive disorders, so that they are rare and they can affect either sex. They are associated with bleeding tendency in women, but no data are available in pregnancy.[4,8,9, 13-15]

## Clinical manifestations

Bleeding history can be of great help in screening women with congenital bleeding disorders: in these women the gynaecological symptoms, such as menorrhagia, being worsened by the defects of haemostasis can suggest the presence of these defects and anticipate possible problems during pregnancy.[1,3,9,13,14] In fact, among 150 women with menorrhagia screened, an inherited bleeding disorder was diagnosed in 26 (17%) patients with the following diagnosis: VWD (n=18), factor XI (n=4), VWD and FXI (n=1), factor X (n=1), haemophilia A carrier (n=1), platelet defect (n=1).[14] Other possible manifestations of an underlying congenital bleeding disorder are methrorrhagia, peritoneal haemorrhage at ovulation, bleeding after miscarriage or abortion or following childbirth (immediate or delayed).[9,13,15,16]

During normal pregnancy, factor VIII and von Willebrand factor (vWF) plasma levels rise spontaneously ,[17] particularly during the third trimester, when levels of factor VIII may double pre-pregnancy value. Pregnancy is accompanied by increased levels of fibrinogen, factor VII and factor X, whereas other clotting factors such as prothrombin, factor V and factor IX do not change significantly.[17] Consequently no particular problems are expected at the time of delivery in haemophilia A carriers and in type 1 VWD patients, who can have a natural vaginal delivery.[18-22] Women with VWD have been reported to be at higher risk of primary (within 24 hours after delivery) and mostly secondary (delayed, from day 2 till 6 week after delivery) post-partum bleeding, particularly in those with type 2 and 3 VWD: VWF and FVIII plasma levels should be checked two-three days after delivery.[15, 16, 19-23] Perineal and vulvar haematomas are other haemorrhagic manifestation of congenital bleeding disorders.[16]

Problems have been reported in the peri-partum period also in patients with other rare congenital bleeding disorders,[16] such as factor XI deficiency (16% of deliveries of a recent cohort),[14, 15] afibrinogenaemia, [3] and carriers of haemophilia B.[24] A recent publication has reported post-partum bleeding in 4 of 5 haemophilia B carriers.[24]

Pregnant carriers of haemophilia can undergo antenatal diagnosis, that can be carried out by chorionic villus sampling from the 11th and the 14th gestational week or by fetal blood sampling from the umbilical cord vein subsequently, both by transabdominal or transvaginal route, under ultrasound guidance. All these methods are invasive and so it is quite possible that in presence of low plasma levels of FVIII or FIX at the time of the procedure can be a cause of maternal bleeding: these clotting factors should be always checked before any invasive action.[19, 25] Consequently abortion and miscarriage in the first 2 trimesters of pregnancy can be accompanied by severe bleeding.

Recurrent miscarriage seems more frequent in women with fibrinogen deficiency, factor XIII deficiency and severe von Willebrand disease, and it can be associated to excessive bleeding.[2, 6, 13, 16, 19, 26]

## Treatment

The treatment and the prophylaxis of bleeding in pregnant women depend on the type of hemostatic defects.[1, 3, 13, 16, 20-23, 27]

Desmopressin in carriers of haemophilia A or women with type 1 VWD can be required when invasive procedures such as antenatal diagnosis (for haemophilia A) or Caesarean section are carried out in presence of plasma clotting factor levels below 40%.[1, 19, 28]

Prolonged treatment with desmopressin, a vasopressin analogue, can cause hyponatraemia, so that sodium concentration should be monitor and water intake restricted.[20] In order to avoid side effects in the newborn, desmopressin can be administered after clamping of the umbilical cord.[1]

Since factor IX levels do not rise significantly in pregnancy, carriers of haemophilia B with a low baseline factor IX level are more likely to require haemostatic support with a FIX concentrate to cover delivery, particularly if a Caesarean section is required, [18, 19, 24] by contrast with the great part of haemophilia A carriers and mild VWD patients.[18] In a retrospective study from Sweden, coagulation factor concentrate was not required in any of 117 pregnancies in carriers of haemophilia, although four mothers required a blood transfusion after delivery.[18] In another, factor VIII was given during pregnancy in only one of 48 pregnancies, and desmopressin in another woman after delivery.[19]

Desmopressin is not able to raise plasma VWF and FVIII levels in women with type 3 VWD, so that all invasive procedures must be avoided and eventually covered with FVIII concentrates, since VWF concentrates are not yet available.[20, 21, 23, 26] In order to provide a better platelet function plasma-derived FVIII concentrates containing high amounts of VWF should be preferred.[29]

Patients with FXI deficiency can bleed at childbirth, but this event is unpredictable, being not correlated with FXI plasma levels: fresh frozen plasma or FXI concentrates should be provided if bleeding occurs or in case of a Caesarean section.[13-16] Patients with fibrinogen or FXIII deficiency should undergo a regular prophylactic replacement therapy during pregnancy and following the childbirth with the deficient clotting factor concentrate (concentrate of fibrinogen and FXIII are available, but they are not licensed in all countries).[1, 6, 16]

There are general principles which can be applied to all type of inherited bleeding disorders, that include clotting factor testing at pregnancy diagnosis, at the end of pregnancy, and every time an invasive procedure is planned, avoiding unnecessary invasive procedures.[1, 3, 16, 20, 21, 27] Epidural anaesthesia might be at risk of bleeding and it should be carried out only when necessary and together with appropriate treatment. Not to forget, the bleeding disorder of the mother can be transmitted to the newborn, so that invasive procedures such as fetal scalp electrodes, ventouse or forcep delivery, troublesome venepuncture and intramuscular injections should be avoided. A blood sample can be obtained from the umbilical cord after clamping for an early diagnosis or for confirmation.

## Conclusions

Clotting factor deficiency must be suspected in women with a bleeding history such as menorrhagia, methrorrhagia, bleeding at ovulation or after miscarriage, abortion, or delivery.[3, 9, 14-16]

Precaution must be taken at delivery in patients with VWD, factor FXI, fibrinogen and FXIII deficiency and in carriers of haemophilia B.[1, 3, 14-16, 24] These women, together with carriers of haemophilia A, are at risk for bleeding when they undergo invasive procedures, such as chorionic villus analysis, fetoscopy, or surgical procedures.[19, 25] Recurrent miscarriage can be observed in women with severe VWD, fibrinogen or FXIII deficiency.[2, 6, 13, 16, 19, 26]

General principles and specific treatment should be followed in order to minimize the risk of bleeding complications. Taking into account existing guidelines, recommendations and isolated experiences,[1, 13, 16, 18-27] it can be stated that:

(a) pregnancy in women with inherited bleeding disorders may require a multidisciplinary approach and consequently they should deliver in a hospital or where there is access to consultants in obstetrics, anaesthesiology, haematology, and paediatrics;

(b) management of pregnant women with congenital bleeding disorders is based on replacement therapy with the deficient clotting factor concentrate when available; desmopressin, platelet transfusion and tranexamic acid are other useful weapons in particular occasions and diseases;

(c) a Caesarean section should be performed for obstetrical indications only;

(d) epidural and spinal anaesthesia are contraindicated unless a plasma level of the deficient factor of 40% is not warranted, whereas regional anaesthesia is not contraindicated if coagulation is normalized;

(e) the risk of early and late postpartum haemorrhage is increased in women with bleeding disorders; excessive postpartum bleeding can occur days after delivery and it must be reported immediately;

(f) forceps, vacuum extraction, and fetal scalp blood sampling should be avoided if the foetus is known or thought to be at risk for a congenital bleeding disorder;

(g) intramuscular injections, surgery, and circumcision should be avoided in neonates at risk for a severe hereditary bleeding disorder until adequate diagnosis and treatment are possible.

In conclusion, congenital bleeding disorders can jeopardize the success of pregnancy if a good liaison with specialized haemostasis centre/expert is not established.

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