

PREGNANCY IN WOMEN WITH INHERITED BLEEDING DISORDERS

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Treatment of Hemophilia Monographs
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Pregnancy in Women with Inherited Bleeding Disorders

Paul L.F. Giangrande

Haemophilia

Haemophilia A is a congenital disorder of coagulation, characterised by deficiency of factor VIII in the blood. Deficiency of factor IX results in an identical clinical condition known as haemophilia B (also known as Christmas disease). Haemophilia is encountered in all racial groups, with an incidence of approximately 1 in 10,000 of the population. The clinical picture is dependent upon the degree of deficiency of the coagulation factor in the blood: severe haemophilia is associated with a level of less than 1% of normal. The hallmark of severe haemophilia is recurrent and spontaneous bleeding into joints, principally the knees, elbows, and ankles. Repeated bleeding into joints can, in the absence of treatment, result in disabling arthritis at an early age. Bleeding into muscles and soft tissues is also seen frequently. Advances in the treatment of haemophilia have led to improvements in both the longevity and quality of life of patients with even severe haemophilia. It is anticipated that the number of patients with severe haemophilia will increase significantly in developed countries, because as people with haemophilia live longer and integrate fully into society, it is more likely that they will raise families and pass the haemophilia gene on to their daughters, who will be carriers. Obstetricians will thus be faced more frequently with managing pregnancies in known or possible carriers of haemophilia.

Carriers of haemophilia

The genes for both factor VIII and IX are located on the X chromosome and thus the inheritance of haemophilia is sex-linked and recessive, like colour blindness. The daughters of men with haemophilia are obligate carriers of the condition, and carriers have a 50:50 chance of passing on the condition to a son and a 50:50

chance that a daughter will be a carrier.

However, one third of cases arise in families with no previous family history, reflecting new mutations. The most famous example of this phenomenon was the British Queen Victoria (1819-1901) who gave birth to a haemophilic son, Leopold, in 1853.

The severity of haemophilia within a given family remains constant. If a woman has relatives with only very mild haemophilia, then she may be reassured that there is no risk of passing on a severe form of the disease to her children.

Most female carriers of haemophilia have levels of factor VIII (or IX) within the normal range but a significant proportion have a modest reduction in the baseline level. 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-to-day 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, such as dental extractions, biopsies, etc. In such circumstances, haemostatic support with desmopressin (DDAVP) or coagulation factor concentrates may be required and the choice of product will depend on both the factor level and the nature of the procedure. Recombinant coagulation factor concentrates should be considered to be the products of choice in such cases because of the potential for transmission of parvovirus B19 with plasma-derived concentrates.

Carrier testing

There is no need to carry out special genetic tests in daughters of men with haemophilia to determine their carrier status as they are obligate carriers. However, genotypic analysis to determine the underlying genetic defect should

be offered as this will facilitate antenatal testing (see below) in due course if required.

The carrier status for other women in an extended family may not be so clear. For example, a woman who has an affected uncle may or may not be a carrier. A pregnant woman with a vague history of a bleeding disorder in a distant relative presents a difficult and all too common problem for obstetricians. Carrier testing can take some months to perform and it may therefore seem logical to start carrier testing as soon as possible in girls with a family history of haemophilia, as this would help the management of pregnancy in the case of an early and unexpected pregnancy. However, in countries where the ethical and/or legal rights of children are protected, testing young children is considered a breach of their rights as they are considered to be too young to give informed consent. These issues must be discussed openly with the family. (A separate monograph by Riva Miller on the topic of genetic counselling is available from the WFH.)

Once the carrier status has been determined and the specific genetic defect has been identified, it is then possible to offer antenatal diagnosis of haemophilia to pregnant women.

Antenatal diagnosis of haemophilia

As a general rule, antenatal diagnosis of haemophilia is only offered where a termination of the pregnancy would be contemplated if an affected fetus were identified. It is certainly not necessary to determine the status of a male fetus simply to plan the management of the pregnancy and delivery. This section aims to present the facts about what techniques are available if antenatal diagnosis is being considered.

It is recognised that social and cultural attitudes to termination of a pregnancy vary considerably around the world. Women will require counselling about haemophilia before they make this important decision. The general experience has been that only a minority of women in developed countries subsequently take up the offer of antenatal diagnosis with a view to termination if an affected fetus is identified (Kadir RA et al, 1997; Tedgård et al, 1999). This

may reflect the fact that many women with affected relatives recognise the tremendous advances in treatment in recent years, including the wider adoption of prophylaxis and the introduction of recombinant products, which have resulted in an essentially normal life for the younger generation of people with haemophilia.

Chorion villus sampling (CVS), or biopsy, is the principal method used for antenatal diagnosis of haemophilia. It offers the major advantage over amniocentesis of permitting diagnosis during the first trimester, although it should not be carried out before 11 weeks of gestation as earlier biopsy may be associated with a risk of subsequent fetal limb abnormalities (Firth HV et al., 1991 and 1994). A sample of chorionic villus is obtained by either the transabdominal or transvaginal route, under ultrasound guidance, and is then subjected to DNA analysis. One disadvantage of this approach is that CVS is performed at a time when the fetal sex is not known, and thus female fetuses are exposed to risk unnecessarily. It is possible that in the not too distant future non-invasive antenatal diagnostic procedures may become available in which fetal DNA can be extracted from fetal normoblasts circulating in the mother's blood (Cheung M-C et al, 1996).

Fetal blood sampling is carried out when it has not been possible to establish the status of the fetus through DNA-based tests. In this technique, fetal blood is taken from fetal umbilical vessels under ultrasound guidance at around 15-19 weeks gestation. Approximately 1 ml of blood is required for assay of coagulation factor levels. The levels of factor VIII and IX in a normal fetus at around 19 weeks gestation are significantly lower than in an adult, at approximately 40 IU/dl and 10 IU/dl respectively (Forestier F et al, 1985 & 1986). It is therefore essential to ensure that the blood is wholly fetal and not contaminated with maternal blood, which could result in diagnostic error through false elevation of the factor level in the sample. This may be done rapidly (during the procedure) by measuring the mean corpuscular volume (MCV) of the erythrocytes with a red cell counter. The fetal MCV is typically at least 120 fl at this stage of pregnancy, while that of

the mother is around 90 fl. However, the Kleihauer technique, based on demonstrating resistance of fetal haemoglobin to acid elution, is more reliable but takes longer to carry out. The factor assay results should never be communicated without results of additional tests to confirm the fetal origin of the sample.

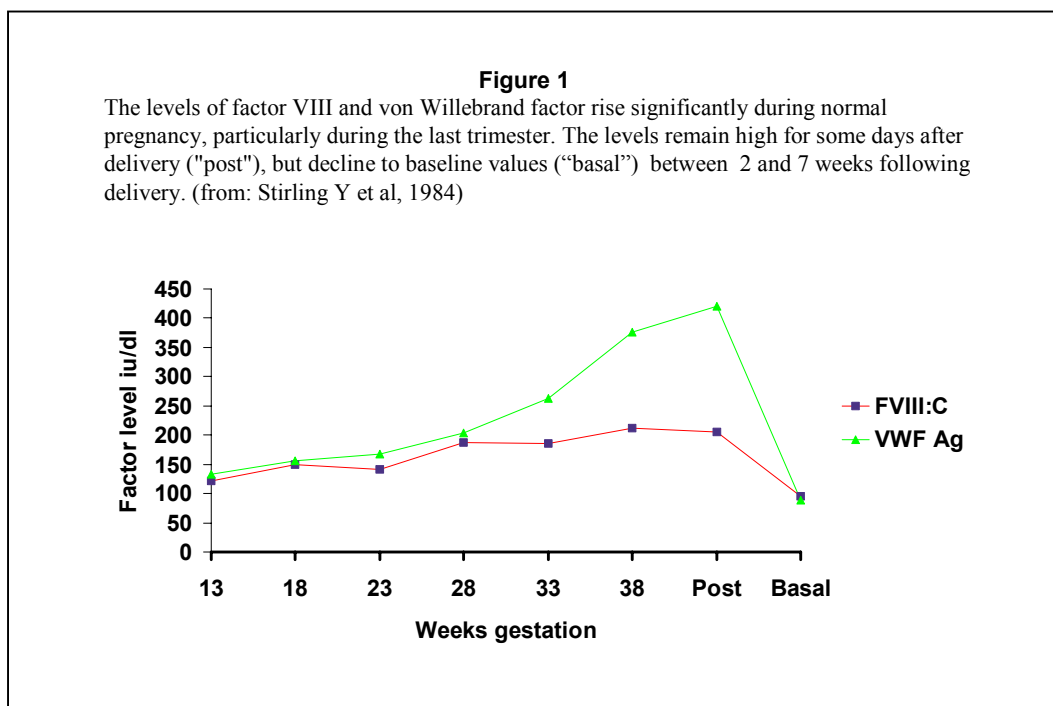
Whatever the method used for antenatal diagnosis, it must be appreciated that the patient is often experiencing enormous psychological stress and turmoil at this time. These needs also need to be addressed and she must not feel under undue pressure from the medical “system” to proceed with a termination.

All invasive methods used for antenatal diagnosis may cause feto-maternal haemorrhage, and anti-D immunoglobulin should be given if the mother is Rh D negative. These procedures are likely to be carried out early in a pregnancy, when the factor VIII level has not risen significantly, and so it is quite possible that some form of haemostatic support may be required to prevent maternal bleeding. It is therefore sensible to check the plasma level of factor VIII (or IX) before the procedure.

Management of pregnancy

The levels of factor VIII and von Willebrand factor (vWF) rise during normal pregnancy (Figure 1). The rise is particularly marked during the third trimester, when levels of factor VIII may be double the normal baseline value. By contrast, factor IX levels do not rise significantly in pregnancy and thus carriers of haemophilia B with a low baseline factor IX level are more likely to require haemostatic support to cover delivery, particularly if a Caesarean section is required. Treatment of carriers of haemophilia A with coagulation factor concentrate is only rarely required during pregnancy. 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 (Ljung R et al, 1994). In another study from London, factor VIII was given during pregnancy in only one of 48 pregnancies, although desmopressin (DDAVP) was given to another woman after delivery (Kadir RA et al, 1997).

The baseline level of factor VIII (or IX) 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, recombinant (genetically engineered) products should be regarded as the products of choice. Plasma-derived products, including those subjected to double viral inactivation processes, have the potential to transmit parvovirus B19. Whilst this is not normally a serious infection in a non-immunocompromised adult, infection of the fetus may result in hydrops fetalis and fetal death. DDAVP is of potential value in these cases, as this chemical can boost the plasma levels of vWF and factor VIII in the blood (Mannucci PM, 1997). However, DDAVP does not boost the level of factor IX in the blood and thus is of no value in carriers of haemophilia B. Manufacturers advise that DDAVP should be used with caution during pregnancy (see section on von Willebrand disease for more detailed discussion). It may be used after delivery, after the umbilical cord has been clamped. It does not pass into breast milk in significant amounts, and so may be given to breastfeeding mothers.

Even though the precise status of the fetus with regard to haemophilia may not have been established through antenatal testing, ultrasound examination during pregnancy to determine the fetal sex is strongly recommended. This may influence decisions in the management of the actual delivery: if the fetus is female it will not have a very low factor VIII level. Even if the mother does not wish to know the result, it is important that this information be available to the obstetrician at the time of delivery.

Delivery

In the past, a Caesarean section was often carried out when there was any doubt about whether a fetus had inherited haemophilia. This is not necessary and vaginal delivery is safe even when the fetus is known to have haemophilia, assuming there are no obstetric contraindications (Ljung R et al, 1994). Epidural anaesthesia is generally permitted if the relevant factor level is at least 40 IU/dl.

Vacuum (Ventouse) extraction should certainly be avoided as the use of this instrument is associated with a high risk of cephalhaematoma or intracranial bleeding. Application of fetal

scalp electrodes to monitor fetal heart rate is also probably best avoided, particularly since external monitors exist which may be used as an alternative.

After delivery, a cord blood sample should be obtained for coagulation factor assay. This opportunity to take a cord blood sample should not be lost. All too frequently, a cord blood sample is not taken and this necessitates subsequent venepuncture of the infant which may be traumatic and result in severe bruising or bleeding, requiring subsequent treatment with blood products. Only 0.5-1 ml of blood is required, collected in citrate tubes. There is no need to send larger samples, which may also make worse any anaemia which the infant may have. There should be clear agreement in advance between clinicians as to who will assume the responsibility of conveying the results to the parents, to avoid misunderstandings. If it is still the hospital's routine practice to administer vitamin K by intramuscular injection, this should be withheld until the result of the factor assay is known or vitamin K should be given orally.

It is not necessary to routinely administer a prophylactic dose of coagulation factor concentrate to a haemophilic newborn after a normal vaginal delivery. However, it is advisable to give an infusion of a coagulation factor concentrate if forceps have been used to assist delivery, and recombinant products should be regarded as the treatment of choice in such circumstances. Coagulation factors VIII and IX do not cross the placenta so a fetus is not protected by infusion of the mother with coagulation factor concentrates during delivery. There is a case report of infusion of recombinant factor VIII by cordocentesis at the onset of labour to cover delivery (Gilchrist GS et al, 2001).

Although it is clear that the risk of intracranial bleeding after a normal vaginal delivery is low (Yoffe G & Buchanan GR, 1988), it is a recognised complication and some consideration should be given to performing an ultrasound scan of the newborn's brain to exclude this possibility.

The obstetrician should be aware of the risk of delayed post-partum haemorrhage in carriers. It is wise to check the factor level a few days after delivery. DDAVP may be useful after delivery.

Summary

The principal points relating to management of pregnancy and delivery are summarised as follows:

1. Good liaison between the haemophilia centre and obstetricians, who may be based in a different hospital, is essential.
2. Baseline factor VIII (or IX) level should be checked at some stage early in the pregnancy, such as during the first consultation with an obstetrician, and in the third trimester (ideally at around 34 weeks).
3. Fetal sex should be determined by ultrasound, and the results should be available to the obstetrician at the time of delivery.
4. Caesarean section is not routinely indicated merely because of possible haemophilia.
5. Epidural anaesthesia is permitted if the factor level is more than 40 IU/dl.
6. Fetal scalp electrodes should not be used for monitoring during delivery.
7. Vacuum extraction (Ventouse delivery) should be avoided.
8. Cord factor level should be checked after birth.
9. Intramuscular vitamin K should be withheld until the result of the factor level is known, or given orally.
10. If forceps are used, the newborn should be given recombinant products (but not routinely otherwise).
11. Special observations after delivery may be warranted, including ultrasound examination

of the head to exclude the possibility of intracranial bleeding.

12. The obstetrician should be aware of the risk of delayed post-partum haemorrhage in carriers. It is wise to check the factor level a few days after delivery. DDAVP may be useful after delivery.

Von Willebrand disease

Von Willebrand factor (vWF) is a protein which is encoded on chromosome 12 and synthesised in endothelial cells. VWF binds to collagen and platelets through the platelet glycoprotein Ib receptor and is essential for platelet adhesion to endothelial cells. VWF also binds circulating factor VIII non-covalently and protects it from degradation and uptake into endothelial cells. Deficiency of vWF, or von Willebrand disease (vWD), typically results in easy bruising, prolonged bleeding from cuts and scratches, epistaxis, and menorrhagia. VWD is inherited as an autosomal dominant condition, and thus children of either sex may inherit the condition. Antenatal diagnosis of vWD is not usually required or requested as the bleeding tendency is relatively mild.

Management of pregnancy

Much of what has been said above about pregnancy in women who are carriers of haemophilia also applies to women with vWD. It is important to establish both the type and plasma levels of factor VIII and vWF for the management of pregnant women with vWD. The level of vWF usually rises to within the normal range by the third trimester and haemostatic support is rarely needed. The level of vWF may not rise significantly during the first or even second trimester and therefore an early miscarriage may be accompanied by significant bleeding. Approximately 80% of all cases of vWD are of the type 1 subtype, characterised by low plasma levels of vWF but qualitatively normal multimers. A concentrate of recombinant vWF concentrate is not yet available but DDAVP (desmopressin) is of potential value in type 1 vWD, as this chemical can boost the plasma levels of vWF and factor VIII in the

blood (Mannucci PM, 1997). However, manufacturers advise that DDAVP should be used with caution during pregnancy. Although DDAVP is theoretically a V₂ agonist devoid of action on smooth muscle, there are case reports of premature labour and hyponatraemia associated with seizures which appear to have been precipitated by intravenous infusion of DDAVP into pregnant women with vWD (Chediak JR et al., 1986). However, anecdotal but unpublished experience with DDAVP in pregnancy suggests that such adverse events are rare, and DDAVP should not be regarded as absolutely contraindicated in pregnancy.

DDAVP is of no value in the other types (2A, 2B, and 3) of vWD, which account for approximately 20% of cases encountered. Type 2B vWD may be associated with a mild and progressive thrombocytopenia and indeed this may lead to the first identification of the disorder. The vWF level in severe (type 3) vWD does not rise significantly at all in pregnancy. If haemostatic support is required in such cases, plasma-derived concentrates which contain vWF will be required: there is no concentrate of recombinant vWF. High-purity (including recombinant) factor VIII concentrates contain no (or very little) vWF and are of no value. Cryoprecipitate also contains vWF, but as it not subjected to viral elimination treatment (e.g., heat treatment) it is not used to treat vWD in developed countries.

Delivery

As a general rule, women with vWD can have a normal vaginal delivery and epidural anaesthesia if their factor VIII level (often used as a surrogate marker for vWF levels) is more than 40 IU/dl and a Caesarean section if their factor VIII level is greater than 50 IU/dl.

Several studies have documented a significantly increased risk of both primary and secondary post-partum haemorrhage in women with vWD, which appears to be higher than in carriers of haemophilia (Ramsahoye RH et al, 1995; Greer IA et al, 1991; Kadir RA et al, 1998). Based on these studies, the risk appears to be relatively higher in women with type 2 vWD as compared with the commoner type 1 vWD. It is thus

prudent to check the vWF level in all women with vWD a few days after delivery. An infusion of DDAVP (desmopressin) may be indicated where the level falls significantly soon after delivery. DDAVP does not pass in significant quantities into breast milk and is therefore safe for breastfeeding mothers.

Severe (type 3) vWD may be readily diagnosed after birth from an umbilical cord blood sample. However, it is almost impossible to diagnose the much commoner, milder forms of vWD in a newborn as the level of vWF rises significantly during birth and an apparently normal result may thus mask a mild form of vWD. Testing is therefore best deferred for some months, unless surgery or some other invasive procedure is necessary in the interim period. It should also be remembered that the expression of vWF is also affected by blood group (individuals with group O having the lowest levels, and those with group AB having the highest) and this can result in variable penetrance of the phenotype (or severity) in a given family (in contrast with haemophilia, where the severity remains constant within a given kindred).

Summary

1. Good liaison between the haemophilia centre and obstetricians, who may be based in a different hospital, is essential.
2. Baseline factor VIII and von Willebrand factor levels should be checked at some stage early in the pregnancy, such as during the first consultation with an obstetrician and in the third trimester (ideally at around 34 weeks).
3. Caesarean section is not routinely indicated merely because of possible vWD.
4. Epidural anaesthesia is permitted if the vWF level is more than 40 IU/dl.
5. Fetal scalp electrodes should not be used for monitoring during delivery.
6. Vacuum extraction (Ventouse delivery) should be avoided.

7. Special observations after delivery may be warranted, including ultrasound examination of the head to exclude the possibility of intracranial bleeding.

The obstetrician should be aware of the risk of delayed post-partum haemorrhage in women with vWD. It is wise to check the factor level a few days after delivery. DDAVP may be useful after delivery.

Other congenital bleeding disorders

Women with congenital deficiencies of other coagulation factors may be encountered occasionally.

Factor I deficiency

Fibrinogen (factor I) is a 340 kD protein encoded on chromosome 4 and synthesised in hepatocytes. Fibrinogen is converted to fibrin through the action of thrombin during the process of coagulation. Fibrinogen is also essential for aggregation of platelets. Afibrinogenaemia may be associated with menorrhagia, recurrent miscarriages, and post-partum haemorrhage. However, regular infusions of fibrinogen concentrate (aiming for a trough fibrinogen level of 1 g/l) may result in a successful outcome (Grech H et al., 1991).

Factor XI deficiency

Factor XI is a serine protease inhibitor, encoded by a gene on chromosome 4, synthesised in hepatocytes. Deficiency of factor XI is associated with a bleeding tendency but there is no correlation between the plasma level and the severity of bleeding. Levels of less than 15% are very likely to be associated with a bleeding tendency, but post-operative bleeding may be seen even in patients with only modest deficiency and levels between 50-70 IU/dl. Factor XI deficiency is particularly common amongst Ashkenazi Jews, but has also been reported in many other ethnic groups. Menorrhagia is a frequent problem in women with factor XI deficiency. The level of factor XI does not rise during pregnancy, in contrast to many other coagulation factors. In view of the unpredictable nature of the bleeding tendency

and the poor correlation with the plasma level of factor XI, labour and delivery should be managed with caution in a centre where fresh frozen plasma can be given promptly if required. In one study of 28 pregnancies in 11 women with factor XI deficiency, the incidence of primary post-partum haemorrhage was 16% (Kadir RA et al, 1998). Prophylactic infusion of plasma may be required, for example to cover a Caesarean section. Cryoprecipitate does not contain factor XI but a lyophilised plasma-derived concentrate of factor XI is available, which has the advantage of having been subjected to a viral elimination treatment. However, this advantage should be balanced against the apparent thrombogenicity of the concentrate. It is probably best reserved for severely deficient women and the post-infusion level should be monitored and maintained below 100 IU/dl.

Factor XIII deficiency

Factor XIII enhances the stability of fibrin clots by forging covalent bonds between adjacent strands of monomeric fibrin. Congenital deficiency of this protein is very rare, but is associated with a very serious bleeding tendency as well as poor wound healing. Early reports in the literature suggested that women with factor XIII deficiency are prone to infertility and/or recurrent miscarriages. However, a programme of regular prophylaxis with regular, monthly infusions of factor XIII concentrates is now usually initiated in developed countries as soon as the condition is diagnosed in childhood and so this problem does not arise. Continued monthly infusions of factor XIII concentrate, aiming for a trough level of not less than 1.5%, is likely to result in a successful outcome in pregnancy (Burrows RF et al, 2000).

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Glossary

Afibrinogenaemia: Congenital deficiency of fibrinogen.

Amniocentesis: A test done during pregnancy to check the fetus for genetic defects. Fluid is taken from the amniotic sac that surrounds the fetus and is sent to a lab for analysis.

Antenatal diagnosis: Diagnosis of genetic disorder during pregnancy.

Baseline factor level: The initial level of a coagulation factor in the blood, prior to the physiological increase associated with pregnancy.

Carrier testing: Genetic testing of possible carriers to identify if they have the gene capable of causing a hereditary condition.

Cephalhaematoma: Extracranial haemorrhage, between the scalp and skull, in an infant.

Chorion villus sampling (CVS): A test done during the first trimester of pregnancy to check the fetus for genetic defects. A sample of chorionic villi, which is tissue in the placenta, is removed and sent to a lab for analysis.

Congenital: Existing at birth. This refers to traits, malformations, diseases, etc. which may be either inherited or due to an influence occurring during gestation.

Contraindication: Any symptom or circumstance that suggests a drug or procedure should not be used, usually because of risk.

Cordocentesis: Drawing a blood sample from the umbilical cord.

Covalent bonds: Type of chemical bond between molecules.

DNA analysis: Examination of the nuclear material contained in the nucleus, which determines the structure of genes and thus also proteins.

Endothelial cells: Cells lining the blood vessels.

Erythrocytes: Red blood cells.

Fibrinogen: Protein converted into insoluble strands of fibrin during the clotting process.

Genotypic analysis: Examination of DNA to determine the sequence of a gene.

Hepatocytes: Liver cells.

Hyponatraemia: Low sodium level.

Intracranial bleeding: bleeding in the brain.

Mean corpuscular volume (MCV): Volume of erythrocyte (red blood cell).

Menorrhagia: heavy menstrual periods.

Monomeric fibrin: Unstable form of fibrin, formed when clot first forms.

Normoblasts: Immature red blood cells (erythrocytes).

Obligate carrier: The daughter of a man with hemophilia. Because she inherits her father's affected X chromosome she is always a carrier.

Platelet glycoprotein Ib receptor: Receptor on the surface of platelets which binds von Willebrand factor.

Serine protease inhibitor: Proteins which inhibit a particular class of proteins, including various coagulation factors.

Thrombogenicity: Potential for inducing thrombus (clot) formation.

V₂ agonist: Receptor on membrane of certain cells, through which DDAVP can stimulate the cell.

Venepuncture: sticking a needle into a vein to draw a blood sample.