Rare Bleeding Disorders

IRISH HAEMOPHILIA SOCIETY

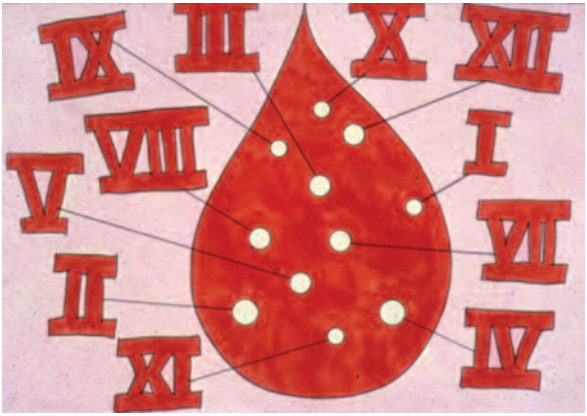
INTRODUCTION

The best known and most common bleeding disorders are Haemophilia A (Factor VIII deficiency), Haemophilia B (Factor IX deficiency) and von Willebrand Disease. However, these do not represent all bleeding disorders. There are a large number of rarer bleeding disorders both of coagulation factors and of platelets. This publication deals with nine disorders affecting coagulation factors I, II, V, VII, X, XI and XIII, in addition to two disorders affecting platelets. Generally the prevalence of these rarer bleedings disorders varies from 1: 100,000 (Factor XI deficiency) to 1: 3 million (Factor XIII deficiency). The prevelance of many of these rare bleeding disorders is higher in Ireland. The reasons for this are not clear, but a small gene pool of large family sizes in the past may be contributory factors. At the time of production of this booklet, there are 443 people with rare bleeding disorders registered with the National Centre for Hereditary Coagulation Disorders in Ireland. These include:

Factor V deficiency	*51 people*
Factor VII deficiency	*61 people*
Factor X deficiency	*70 people*
Factor XI deficiency	*93 people*
Factor XIII deficiency	*4 people*
Bernard Soulier Syndrome	*3 people*
Glanzmann Thrombasthenia	*9 people*
Unknown rare bleeding disorders	*363 people*

We hope you find the information in this booklet practical and useful.

Brian O'Mahony
Chief Executive



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WHAT ARE CLOTTING FACTORS?

Clotting factors are proteins in the blood that control bleeding. When a blood vessel is injured, the walls of blood vessels contract to limit the flow of blood to the damaged area. Small blood cells called platelets are then activated and stick to the site of injury and spread along the surface of the blood vessel to stop bleeding.

At the same time, chemical signals are released from small sacs inside the platelets that attract other cells to the area which make them clump together to form what is called a platelet plug.

On the surface of these platelets, many different clotting factors work together in a series of complex chemical reactions (known as the coagulation cascade) to form a fibrin clot. The clot acts like a mesh to stop the bleeding.

Coagulation factors circulate in the blood in an inactive form. When a blood vessel is injured, the coagulation cascade is initiated and each coagulation factor is activated in a specific order to lead to the formation of the blood clot. Coagulation factors are identified with Roman numerals (e.g. Factor I or FI).

WHAT ARE RARE CLOTTING FACTOR DEFICIENCIES?

If any of the clotting factors are missing or are not working properly, the coagulation cascade is blocked. When this happens, the blood clot does not form and the bleeding continues for longer than it should.

Deficiencies of Factor VIII and Factor IX are known as Haemophilia A and B, respectively. Rare clotting factor deficiencies are bleeding disorders in which one or more of the other clotting factors (i.e. Factors I, II, V, V+VIII, VII, X, XI, or XIII) is missing or not working properly. Less is known about these disorders because they are diagnosed so rarely. In fact, many have only been discovered in the last 40 years.

HOW DOES CLOTTING WORK NORMALLY?

Blood is carried throughout the body in a network of blood vessels. When tissues are injured, damage to a blood vessel may result in leakage of blood through holes in a vessel wall. The vessels can break near the surface, as in the case of a cut. They can also break deep inside the body, causing a bruise or an internal haemorrhage.

Clotting, or coagulation, is a complex process that makes it possible to stop injured blood vessels from bleeding.

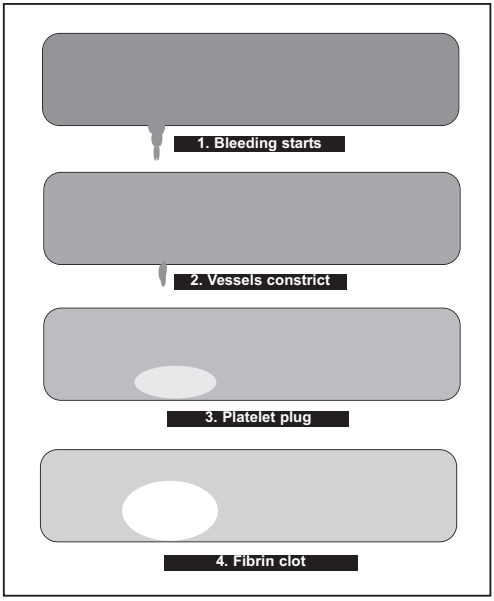


Figure 1: Forming a Clot

Figure 1 shows the four steps involved in forming a plug:

Step 1: The blood vessel is damaged.

Step 2: The blood vessels contract to restrict the blood flow to damaged area.

Step 3: Blood platelets, which are tiny cell fragments, are the first to arrive at the damaged area. The platelets stick to the walls of damaged vessels and spread out, this is called platelet adhesion. These platelets then emit chemical signals that activate other nearby platelets so that they clump together at the site of the damage in order to form a plug, the hemostatic plug. This is called platelet aggregation.

Step 4: The surface of these activated platelets forms a base on which blood coagulation can take place. The coagulation factors (or coagulation proteins) circulating in the blood are activated at the surface of the platelets to form a fibrin clot which looks something like a mesh. This is the permanent clot.

These factors (Factors I, II, V, VIII, IX, X, XI, XII and XIII) are triggered in a kind of domino effect, a chain reaction that is called the coagulation cascade.

Figure 2 on the next page shows the stages in clot formation in a way that makes it easier to understand the clotting cascade.

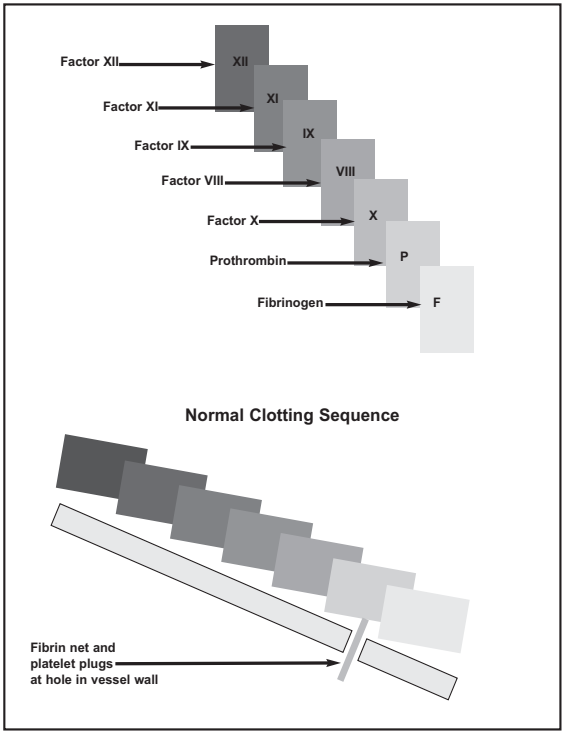


Figure 2: Domino Effect of Clotting Cascade

HOW ARE BLEEDING DISORDERS INHERITED?

Bleeding disorders are generally passed from parent to child at the time of conception. Each cell of the body contains structures called chromosomes. A chromosome is a long chain of chemicals known as DNA. This DNA is arranged into about 30,000 units called genes. These genes determine such things as the colour of a person's eyes. In the case of factor deficiencies, one of these genes has a defect. The defective gene that causes a factor deficiency is usually on a chromosome, which does not decide the sex of the child. This means the bleeding disorder is an autosomal inherited pattern and can affect females as well as males. The majority of bleeding disorders have an autosomal inheritance pattern. These are Factor I, II, V, VII, X, XI, XII, XIII, vWD and platelet function disorders.

AUTOSOMAL INHERITED BLEEDING DISORDERS

There are two types of autosomal inheritance patterns, autosomal recessive and autosomal dominant. Autosomal dominant means that only one defective gene, from one of the child's parents is required in order for the disorder to affect the child. Autosomal recessive means that each parent must pass on a defective gene in order for the child to manifest the disorder.

When only one of the two parents is a carrier of the gene and it is passed on to a child, the child will not be affected. A carrier is someone who carries the defective gene without being affected by the disorder. In order for a person to be affected by a specific factor deficiency, he or she must have inherited two defective genes, one from the mother and one from the father. Both parents must therefore be carriers. If a person inherits the defective gene from only one of the parents, he/she will be a carrier. His/her specific factor level will be lower than normal. Symptoms of the disease may be absent or only slightly present. The majority of bleeding disorders have an autosomal recessive inheritance pattern. The following five illustrations show how a factor deficiency can be passed on for each pregnancy with autosomal inherited bleeding disorders.

Figure 3 shows what can happen when both parents are carriers. There is one chance that the child will be normal, one chance that it will have the disorder, and there are two possibilities that the child will be a carrier.

Figure 3: Both parents are carriers of the deficiency

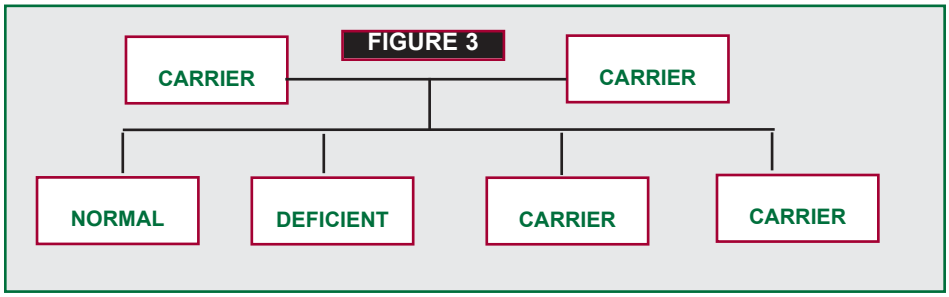


Figure 4 shows what can happen when both parents have a defective gene deficiency. All their children will also have the same deficiency.

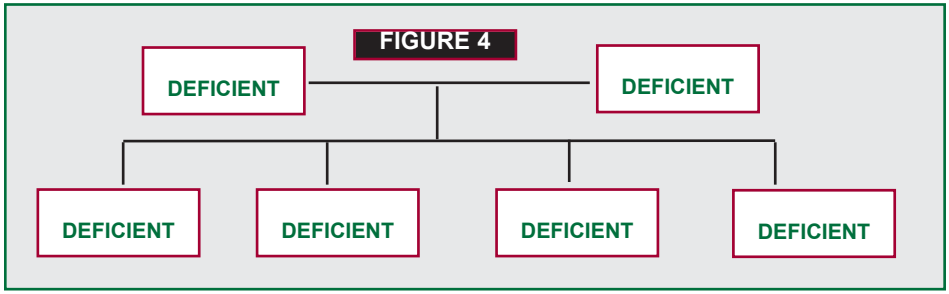


Figure 4: Both parents have the factor deficiency

Figure 5 shows what can happen when one of the parents has the disorder and the other is normal. All their children will be carriers of the specific factor deficiency.

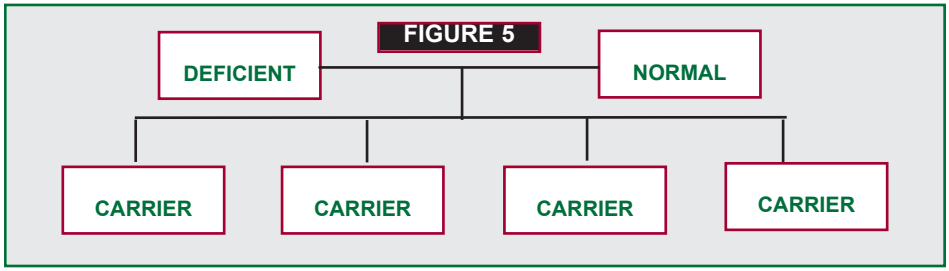


Figure 5: One parent has the deficiency

Figure 6 shows what can happen when one of the parents is a carrier and the other is normal. There are two possibilities that the child will be a carrier and two possibilities that it will be normal.

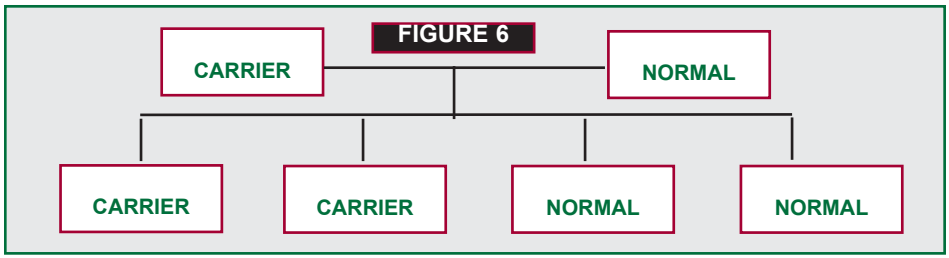


Figure 6: One parent is a carrier

Figure 7 shows what can happen when one of the parents has the disorder and the other is a carrier. There are 2 possibilities that the child will have the disorder and 2 possibilities that it will be a carrier.

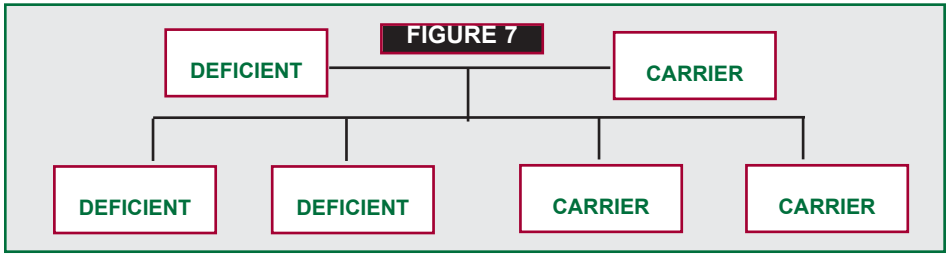


Figure 7: One parent has a deficiency and the other is a carrier

*[**Note:** Some rare bleeding disorders (II, X, XIII, BSS) have another forms of the deficiency that is not inherited but is acquired. There are various causes. These bleeding disorders are also extremely rare.]*

FACTOR I (FIBRINOGEN) DEFICIENCY

Factor I (also called Fibrinogen) deficiency is an inherited bleeding disorder that is caused by a problem with Factor I. Because the body produces less Fibrinogen than it should, or because the Fibrinogen is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor I deficiency is an umbrella term for several related disorders known as congenital Fibrinogen defects. Afibrinogenemia (a lack of Fibrinogen) and hypofibrinogenemia (low levels of Fibrinogen) are quantitative defects, meaning the amount of Fibrinogen in the blood is abnormal. Dysfibrinogenemia is a qualitative defect in which Fibrinogen does not work the way it should. Hypodysfibrinogenemia is a combined defect that involves both low levels of Fibrinogen and impaired function.

Afibrinogenemia is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child.

Hypofibrinogenemia, dysfibrinogenemia, and hypodysfibrinogenemia can be either recessive (both parents carry the gene) or dominant (only one parent carries and transmits the gene).

All types of Factor I deficiency affect both males and females.

SYMPTOMS

The symptoms of Factor I deficiency differ depending on which form of the disorder a person has.

AFIBRINOGENEMIA

Common symptoms

- nosebleeds (epistaxis)
- easy bruising
- heavy or prolonged menstrual bleeding (menorrhagia)
- muscle bleeds
- bleeding into joints (hemarthrosis)
- bleeding from the umbilical cord stump at birth
- bleeding in the mouth, particularly after dental surgery
- abnormal bleeding during or after injury, surgery, or childbirth
- abnormal bleeding after circumcision
- problems during pregnancy (including miscarriage)

Other reported symptoms

- bleeding in the gut (gastrointestinal haemorrhage)
- bleeding in the central nervous system (the brain and spinal cord)
- formation of blood clots (thrombosis)

HYPOFIBRINOGENEMIA

Symptoms are similar to those seen in afibrinogenemia. As a general rule, the less Factor I a person has in his/her blood, the more frequent and/or severe the symptoms.

DYSFIBRINOGENEMIA

Symptoms depend on how the Fibrinogen (which is present in normal quantities) is functioning. Some people have no symptoms at all. Other people experience bleeding (similar to those seen in afibrinogenemia) and others show signs of thrombosis (abnormal blood clots in blood vessels) instead of bleeding.

HYPODYSFIBRINOGENEMIA

Symptoms are variable and depend on the amount of Fibrinogen that is produced and how it is functioning.

DIAGNOSIS

Factor I deficiency is diagnosed by a variety of blood tests, including a specific test that measures the amount of Fibrinogen in the blood. However, low Fibrinogen levels or abnormal function may be a sign of another disease. Diagnostic tests should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre. An explanation of these tests are outside the scope of this publication.

TREATMENT

There are three treatments available for Factor I deficiency. All are made from human plasma:

1. Fibrinogen concentrate
2. Cryoprecipitate
3. Fresh frozen plasma (FFP)

Treatment may also be given to prevent the formation of blood clots, as this complication can occur after Fibrinogen replacement therapy.

Many people who have hypofibrinogenemia or dysfibrinogenemia do not need treatment. Excessive menstrual bleeding in women with Factor I deficiency may be controlled with hormonal contraceptives or antifibrinolytic drugs.

[For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

FACTOR II (PROTHROMBIN) DEFICIENCY

Factor II (also called Prothrombin) deficiency is an inherited bleeding disorder. Because the body produces less prothrombin than it should, or because the prothrombin is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor II deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. Factor II deficiency is very rare.

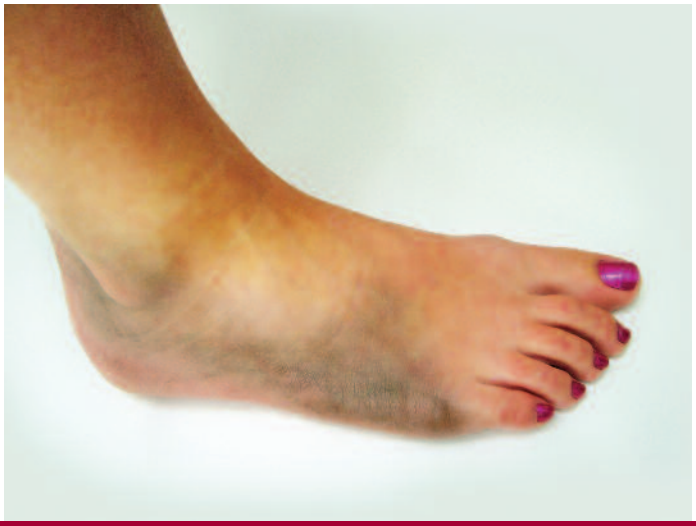
Factor II deficiency may be inherited with other factors deficiencies (see "Combined deficiency of vitamin K-dependent clotting factors" on page 18). It can also be acquired later in life as a result of liver disease, vitamin K deficiency, or certain medications such as the blood thinning drug Coumadin®. Acquired Factor II deficiency is more common than the inherited form.

SYMPTOMS

The symptoms of Factor II deficiency are different for everyone. The less Factor II a person has in his/her blood, the more frequent and/or severe the symptoms.

Common symptoms

- nosebleeds (epistaxis)
- easy bruising
- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding into joints (hemarthrosis)
- muscle bleeds
- bleeding in the mouth, particularly after dental surgery



Other reported symptoms

- bleeding in the gut (gastrointestinal haemorrhage)
- bleeding from the umbilical cord stump at birth
- abnormal bleeding during or after injury, surgery, or childbirth

Rare symptoms

- bleeding in the central nervous system (the brain and spinal cord)
- blood in urine (hematuria)

DIAGNOSIS

Factor II deficiency is diagnosed by a variety of blood tests. The doctor will need to measure the amount of Factors II, V, VII, and X in the blood. Diagnostic tests should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre.

TREATMENT

There are two treatments available for Factor II deficiency. Both are made from human plasma.

1. Prothrombin complex concentrate (PCC)
2. Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with Factor II deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

[For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

FACTOR V DEFICIENCY

Factor V deficiency is an inherited bleeding disorder. Because the body produces less Factor V than it should, or because the Factor V is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form. Factor V deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. Factor V deficiency is very rare.

SYMPTOMS

The symptoms of Factor V deficiency are generally mild. Some people may experience no symptoms at all. However, children with a severe deficiency of Factor V may bleed very early. Some patients have experienced bleeding in the central nervous system (the brain and spinal cord) very early in life.

Common symptoms

- nosebleeds (epistaxis)
- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding in the mouth, particularly after dental surgery

Other reported symptoms

- bleeding in the gut (gastrointestinal haemorrhage)
- muscle bleeds
- abnormal bleeding during or after injury, surgery, or childbirth

Rare symptoms

- bleeding into joints (hemarthrosis)
- bleeding in the central nervous system (the brain and spinal cord)

DIAGNOSIS

Factor V deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre. People with abnormal levels of Factor V should also have their Factor VIII levels checked to rule out combined Factor V and Factor VIII deficiency, which is a completely separate disorder.

TREATMENT

Treatment for Factor V deficiency is usually only needed for severe bleeds or before surgery. Fresh frozen plasma (FFP) is used because there is no concentrate containing only Factor V available. Platelet transfusions are sometimes an option.

Excessive menstrual bleeding in women with Factor V deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

[For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

COMBINED FACTOR V AND FACTOR VIII DEFICIENCY

Combined Factor V and Factor VIII deficiency is an inherited bleeding disorder that is caused by low levels of Factors V and VIII. Because the amount of these factors in the body is lower than normal, the clotting reaction is blocked prematurely and the blood clot does not form. The combined deficiency is completely separate from Factor V deficiency and Factor VIII deficiency (Haemophilia A). Combined Factor V and Factor VIII deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. The deficiency is very rare. Normally the disorder is caused by a single gene defect that affects the body's ability to transport Factor V and Factor VIII outside the cell and into the bloodstream, and not by a problem with the gene for either factor.

SYMPTOMS

The combination of Factor V and Factor VIII deficiency does not seem to cause more bleeding than if only one or the other of the factors were affected. The symptoms of combined Factor V and Factor VIII deficiency are generally mild.

Common symptoms

- skin bleeding
- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding in the mouth, particularly after dental surgery
- bleeding after circumcision
- abnormal bleeding during or after injury, surgery, or childbirth

Other reported symptoms:

- nosebleeds (epistaxis)

Rare symptoms

- bleeding into joints (hemarthrosis)
- muscle bleeds

DIAGNOSIS

Combined Factor V and Factor VIII deficiency is diagnosed by a variety of blood tests to determine if the levels of both factors are lower than normal. These tests should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre.

TREATMENT

There are three treatments available for combined Factor V and Factor VIII deficiency.

1. Factor VIII concentrate
2. Fresh frozen plasma (FFP)
3. Desmopressin (DDAVP)

Excessive menstrual bleeding in women with combined Factor V and Factor VIII deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

 [For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

FACTOR VII DEFICIENCY

Factor VII deficiency is an inherited bleeding disorder that is caused by a problem with Factor VII. Because the body produces less Factor VII than it should, or because the Factor VII is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form. This is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also affects both males and females. Factor VII deficiency is very rare. Factor VII deficiency may be inherited with other factor deficiencies *(see "Combined deficiency of vitamin K dependent clotting Factors" on page 18).* It can also be acquired later in life as a result of liver disease, vitamin K deficiency, or certain medications such as the blood thinning drug Coumadin®.

SYMPTOMS

The symptoms of Factor VII deficiency are different for everyone. Generally, the less Factor VII a person has, the more frequent and/or severe the symptoms. People with very low levels of Factor VII can have very serious symptoms.

Common symptoms

- nosebleeds (epistaxis)
- easy bruising
- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding in the mouth, particularly after dental surgery
- bleeding in the head (newborns)
- heavy bleeding at circumcision

Other reported symptoms

- bleeding in the gut (gastrointestinal bleeding)
- bleeding into joints (hemarthrosis)
- muscle bleeds
- bleeding in the central nervous system (the brain and spinal cord)
- abnormal bleeding during or after injury, surgery, or childbirth

Rare symptoms

- blood in urine (hematuria)
- bleeding from the umbilical cord stump at birth

DIAGNOSIS

Factor VII deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre.

TREATMENT

There are several treatments available for Factor VII deficiency.

1. Recombinant Factor VIIa concentrates (rFVIIa)
2. Plasma derived Factor VII concentrate
3. Prothrombin complex concentrate (PCC) containing Factor VII
4. Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with Factor VII deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

[For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

FACTOR X DEFICIENCY

Factor X deficiency is an inherited bleeding disorder. Because the body produces less Factor X than it should, or because the Factor X is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form. Factor X deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. Factor X deficiency is one of the rarest inherited clotting disorders. Factor X deficiency may also be inherited with other factor deficiencies. (see "Combined deficiency of vitamin K dependent clotting factors" on page 18).

SYMPTOMS

The less Factor X a person has in his/her blood, the more frequent and/or severe the symptoms. People with severe Factor X deficiency can have serious bleeding episodes.

Common symptoms

- nosebleeds (epistaxis)
- bleeding in the gut (gastrointestinal haemorrhage)
- bleeding into joints (hemarthrosis)
- muscle bleeds
- bleeding from the umbilical cord stump at birth
- bleeding from the mouth, particularly after dental surgery
- bleeding during or after surgery or injury

Other reported symptoms

- heavy or prolonged menstrual bleeding (menorrhagia)
- bleeding after circumcision
- abnormal or prolonged bleeding after childbirth
- first-trimester miscarriage (spontaneous abortion)
- blood in urine (hematuria)
- bleeding in the central nervous system (the brain and spinal cord)

DIAGNOSIS

Factor X deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre.

TREATMENT

There are two treatments available for Factor X deficiency. Both are made from human plasma.

1. Prothrombin complex concentrate (PCC) containing Factor X
2. Factor X concentrate, containing some Factor IX
3. Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with Factor X deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

 [For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

COMBINED DEFICIENCY OF VITAMIN K - DEPENDENT CLOTTING FACTORS

Inherited combined deficiency of the vitamin K dependent clotting factors (VKCFD) is a very rare inherited bleeding disorder that is caused by a problem with clotting Factors II, VII, IX, and X. In order to continue the chain reaction of the coagulation cascade, these four factors need to be activated in a chemical reaction that involves vitamin K. When this reaction does not happen the way it should, the clotting reaction is blocked and the blood clot does not form. VKCFD is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. VKCFD is very rare. VKCFD can also be acquired later in life as a result of other disorders, or certain medications such as the blood thinning drug Coumadin®. Acquired VKCFD is more common than the inherited form. Some newborn babies have a temporary vitamin K deficiency, which can be treated with supplements at birth.

SYMPTOMS

The symptoms of VKCFD vary a great deal from one individual to another but are generally mild. The first symptoms may appear at birth. Symptoms at birth must be differentiated from the acquired deficiency. People with severe deficiencies can have serious bleeding episodes.

Reported symptoms

- bleeding from the umbilical cord stump at birth
- bleeding into joints (hemarthrosis)
- bleeding in soft tissue and muscle
- bleeding in the gut (gastrointestinal haemorrhage)
- easy bruising
- excessive bleeding after surgery

Rare symptoms

- bleeding in the brain (intracranial haemorrhage)
- skeletal abnormalities and mild hearing loss (in severe cases)

DIAGNOSIS

VKCFD is diagnosed by a variety of blood tests that should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre. Care should be taken, particularly in newborns, to exclude causes of acquired vitamin K deficiency or exposure to certain medications.

TREATMENT

There are three treatments available for VKCFD.

1. Vitamin K
2. Prothrombin complex concentrates (PCC)
3. Fresh frozen plasma (FFP)

[For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

FACTOR XI DEFICIENCY

Factor XI deficiency is an inherited bleeding disorder. Because the body produces less Factor XI than it should, or because the Factor XI is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form.

Factor XI deficiency is also called Haemophilia C. It differs from Haemophilia A and B in that there is no bleeding into joints and muscles. Factor XI deficiency is the most common of the rarer bleeding disorders and the second most common bleeding disorder affecting women (after von Willebrand disease).

SYMPTOMS

Most people with Factor XI deficiency will have little or no symptoms at all. The relationship between the amount of Factor XI in a person's blood and the severity of his/her symptoms is unclear; people with only a mild deficiency in Factor XI can have serious bleeding episodes. Symptoms of Factor XI deficiency vary widely, even among family members, which can make it difficult to diagnose.

Common symptoms

- nosebleeds (epistaxis)
- easy bruising
- heavy or prolonged menstrual bleeding (menorrhagia)
- abnormal bleeding during or after injury, surgery, or childbirth

Other reported symptoms

- bleeding in the gut (gastrointestinal haemorrhage)
- bleeding in the mouth, particularly after dental surgery
- blood in the urine (hematuria)

DIAGNOSIS

Factor XI deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre.

TREATMENT

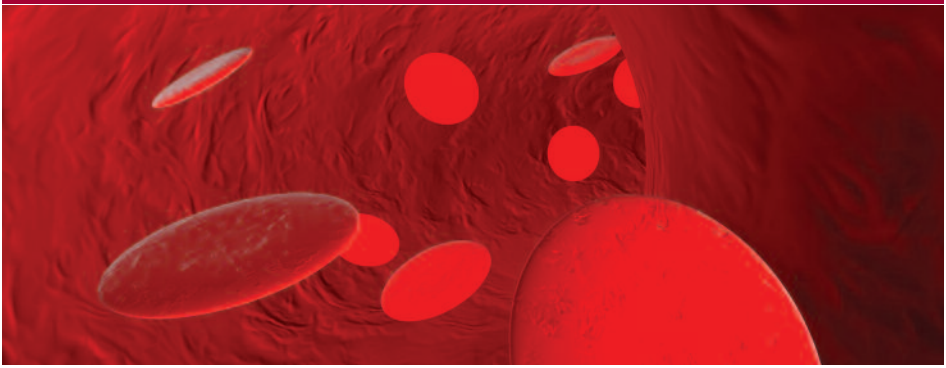
There are several treatments available to help control bleeding in people with Factor XI deficiency.

1. Factor XI concentrate
2. Antifibrinolytic drugs
3. Fibrin glue
4. Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with Factor XI deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

[For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

FACTOR XIII DEFICIENCY



Factor XIII deficiency is an inherited bleeding disorder. Because the body produces less factor XIII than it should, or because the Factor XIII is not working properly, the clotting reaction is blocked prematurely and the blood clot does not form. Factor XIII deficiency is an autosomal recessive disorder, which means that both parents must carry the defective gene in order to pass it on to their child. It also means that the disorder affects both males and females. Factor XIII deficiency is very rare.

SYMPTOMS

Most people with Factor XIII deficiency experience symptoms from birth, often bleeding from the umbilical cord stump. Symptoms tend to continue throughout life. As a general rule, the less Factor XIII a person has in his/her blood, the more frequent and/or severe the symptoms.

Common symptoms

- bleeding from the umbilical cord stump at birth
- nosebleeds (epistaxis)
- easy bruising
- bleeding into joints (hemarthrosis)
- bleeding in the central nervous system (the brain and spinal cord)
- bleeding in the mouth, particularly after dental surgery
- poor wound healing and abnormal scar formation
- bleeding in soft tissue
- problems during pregnancy (including recurrent miscarriages)
- bleeding after circumcision
- abnormal bleeding during or after injury or surgery

Other reported symptoms

- heavy or prolonged menstrual bleeding (menorrhagia)
- blood in urine (hematuria)
- bleeding in the gut (gastrointestinal hemorrhage)
- muscle bleeds

Rare symptoms

- bleeding in the spleen, lungs, ears, or eyes.

DIAGNOSIS

Factor XIII deficiency is difficult to diagnose. Standard blood clotting tests do not detect the deficiency, and many laboratories are not equipped with more specialised tests that measure the amount of Factor XIII in a blood sample or how well Factor XIII is working. The high rate of bleeding at birth usually leads to early diagnosis.

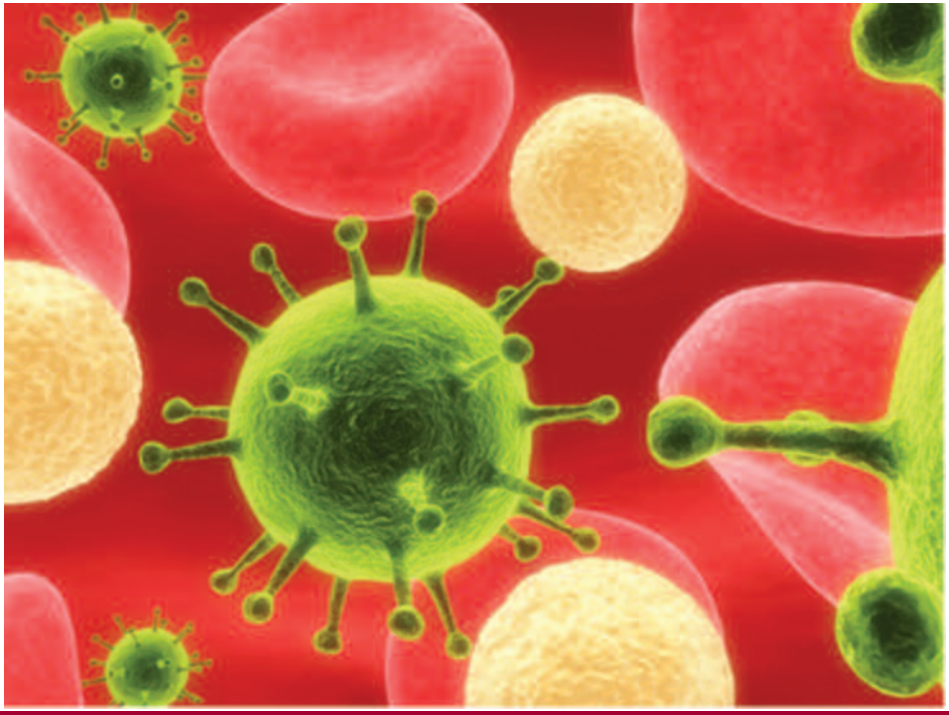
TREATMENT

There are several treatments available to help control bleeding in people with Factor XIII deficiency.

1. Factor XIII concentrate
2. Cryoprecipitate
3. Fresh frozen plasma (FFP)

Excessive menstrual bleeding in women with Factor XIII deficiency may be controlled with hormonal contraceptives (birth control pills) or antifibrinolytic drugs.

[For more information on TREATMENT OPTIONS, turn to Page 23 & 24]



BERNARD - SOULIER SYNDROME (BSS)

Bernard - Soulier Syndrome (BSS) is extremely rare. It has been estimated that this disorder affects less than one person in a million. BSS is a blood clotting disorder that hinders the ability of blood platelets to stick together and spread around a broken vessel.

Patients with BSS have an insufficient number of platelets. In addition, their platelets are larger than normal and do not function properly. The disorder is caused by a deficiency in a protein found on the surface of platelets. This protein is essential to the aggregation of platelets around injured blood vessels and a deficiency prolongs bleeding episodes because platelets fail to form a clot.

SYMPTOMS

People with BSS show signs of abnormal bleeding episodes during their first year of life and symptoms can be:

Common symptoms

- Bruising
- Nosebleed
- Bleeding from the mouth
- Menorrhagia (heavy menstrual flow)

Rare symptoms

- Bleeding in the urinary tract
- gastrointestinal tract

DIAGNOSIS

BSS is diagnosed by a variety of blood tests that should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre.

TREATMENT

There are two treatment options for severe bleeding a platelet transfusion or the administration of recombinant Factor VIIa may be used. Tranexamic acid helps hold the clot in place after it has formed. It has proven very useful in controlling mucosal bleeding (bleeding of soft tissues, such as the mouth or nose).

[For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

GLANZMANN THROMBASTHENIA

Glanzmann Thrombasthenia affects the ability of the blood platelets to gather around the site of a broken blood vessel. The platelets are sometimes present in normal quantities but are unable to work normally. This protein is needed so that platelets aggregate around an injury to a blood vessel.

Because of the deficiency, platelets fail to form a plug to stop the bleeding. Glanzmann Thrombasthenia has three categories of severity.

Type I (Severe) is an individual with level less than 5% of normal.

Type II (Less severe) is an individual with between 5% and 20% of normal.

Type III (Least severe)is a variant of Thrombasthenia with levels of more than 50% of normal, but with major abnormalities in the way platelets aggregate.

SYMPTOMS

People with Glanzmann Thrombasthenia can have the following symptoms:

Common symptoms

- Nosebleeds
- Bruising
- Gastrointestinal bleeding
- Increased and longer menstrual bleeding

Other symptoms

- Spontaneous abortion in the first quarter
- Bleeding during and after Surgery or Trauma

DIAGNOSIS

Glanzmann Thrombasthenia deficiency is diagnosed by a variety of blood tests that should be performed by a specialist at a Haemophilia/Bleeding Disorders Treatment Centre.

TREATMENT

Prolonged pressure at the site of a cut on the skin or in the mouth and packing in the nose in the event of a nose bleed (epistaxis). Tranexamic acid is used to stop clots from being broken down. In the case of severe bleeds intravenous transfusion of platelets may be required. This treatment is limited by the appearance of antibodies that destroy the transfused platelets. Recombinant Factor VIIa may also be used in certain cases.

[For more information on TREATMENT OPTIONS, turn to Page 23 & 24]

TREATMENT OPTIONS

FACTOR CONCENTRATES

Factor concentrates are the ideal and safest treatment for rare bleeding disorders. Currently concentrates are available for Factors I, VII, VIII, X, XI, and XIII. Factor concentrates for rare bleeding disorders are usually made from human plasma. Recombinant Factor VIII and recombinant Factor VIIa are also available. Factor concentrates are administered intravenously.

PROTHROMBIN COMPLEX CONCENTRATE (PCC)

This concentrate is made from human plasma and contains a mixture of clotting factors, including Factors II, VII, IX, and X (however, some products do not contain all four factors). PCC is suitable for individual deficiencies of Factor II and X as well as inherited combined deficiency of the vitamin K dependent clotting factors (VKCFD). PCC is administered intravenously.

FRESH FROZEN PLASMA (FFP)

Plasma is the portion of blood that contains clotting factor, as well as other blood proteins. FFP is used to treat rare bleeding disorders when concentrates of the specific factor that is missing are not available. FFP is the usual treatment for Factor V deficiency. FFP is administered intravenously.

CRYOPRECIPITATE

Made from human plasma, cryoprecipitate contains Factor VIII, Fibrinogen (Factor I), and a few other proteins important for blood clotting. It contains higher concentrations than FFP of some (but not all) coagulation factors, so less volume is needed. It is only suitable for a few deficiencies. Cryoprecipitate is administered intravenously.

DESMOPRESSIN

Desmopressin is a synthetic hormone that raises the levels of Factor VIII in patients with combined Factor V and Factor VIII deficiency. Desmopressin has no effect on the levels of any of the other coagulation factors. It can be administered intranasally or intravenously.

ANTIFIBRINOLYTIC DRUGS

The antifibrinolytic drugs tranexamic acid and aminocaproic acid are used to hold a clot in place in certain parts of the body, such as the mouth, bladder, and uterus. They are also very useful in many situations, such as during dental work, but are not effective for major internal bleeding or surgery. Antifibrinolytic drugs are particularly useful for patients with Factor XI deficiency. They are also used to help control excessive menstrual bleeding. Antifibrinolytic drugs can be administered orally or by injection.

FIBRIN GLUE

Fibrin glue can be used for dental work or to treat external wounds. It is not used for major bleeding or surgery. It is applied to the bleeding site.

PLATELET TRANSFUSIONS

Platelets are small blood cells that are involved in the formation of blood clots and the repair of damaged blood vessels. Certain clotting factors, including Factor V, are stored in small sacs inside them. Platelet transfusions are sometimes used to treat Factor V deficiency.

VITAMIN K

Treatment with vitamin K (either in pill form or by injection) can help control symptoms of inherited combined deficiency of the vitamin K dependent clotting factors (VKCFD). However, not everyone responds to this type of treatment. People who do not respond to vitamin K and have a bleed or need surgery will need factor replacement.

HORMONAL CONTRACEPTIVES

Hormonal contraceptives (birth control pills) help control menstrual bleeding.

BASIC TREATMENT FOR BLEEDING EPISODES

This section describes how to treat minor or moderate bleeds in joints or in soft tissues. **It is not a substitute for medical treatment such as Factor Replacement Therapy, but can be beneficial.** The basic first aid for any bleed is Rest, Ice, Compression, Elevation. These four steps are known as R.I.C.E and can help to reduce pain and discomfort of a bleed.

Rest - Rest a limb by using crutches or a wheelchair. Minimise walking as much as possible. Rest an arm by using a sling to support the limb.

Ice - Apply ice to the injured site. Use an ice pack or a bag of frozen peas wrapped in a damp towel. Never apply the ice directly to the skin. Apply the ice for about 15 minutes every 2 hours.

Compression - Wrap an injured joint in an elastic bandage using a figure eight pattern. Watch for signs of numbness, cold, sharp pain, or a change of colour in the finger or toes. These are signs that the circulation has been cut off. If any of these signs occur, remove the bandage and reapply it with less tension.

Elevation – Raise the affected limb above the heart to reduce swelling. This will also improve blood circulation.

The Haemophilia Treatment Centre (HTC) team will provide support during these bleeding episodes. A major bleed into a muscle can cause permanent damage to the affected limb and be extremely painful. If a muscle bleed is suspected contact your HTC as soon as you can.

[These treatments may have side effects, therefore it is very important to talk to your physician about treatment options.]

RECOGNISING BLEEDING

It is important that people who have rare bleeding disorders learn to recognise the signs and symptoms of a bleeding episode that can threaten their lives or the permanent functionality of a limb so that they can react as soon as possible with the correct treatment. People with mild to moderate deficiencies should pay special attention to this as they are rarely affected by symptoms and as a result, they may be more at risk of not recognising a major bleed. The following information describes the main kinds of bleeding that can occur in persons affected by coagulation disorders.

TYPE OF BLEEDING	SIGNS AND SYMPTOMS	RECOMMENDATIONS
HEAD (bleeding in the brain is very serious)	• headache • blurred or double vision • nausea and vomiting • mood or personality changes • drowsiness • loss of balance • loss of fine motor coordination • loss of consciousness • seizures	All unusual signs and symptoms should be reported to the medical team preferably at the HTC so treatment can be given as soon as possible.
NECK	• pain in the neck or throat • swelling • difficulty swallowing • difficulty breathing	A throat infection could cause bleeding. This type of bleeding is rare.
CHEST	• pain in the chest • difficulty breathing • coughing, blood in spittle	This kind of bleeding is extremely rare.
ABDOMEN (stomach)	• pain in the abdomen or lower back • nausea or vomiting • blood in the urine • blood in the stool or black stool	All signs and symptoms of this nature should be reported to the medical team so treatment can be provided as soon as possible.
SOFT TISSUE	• redness in the affected area • a bruise increases in size (hematoma) • pain	
JOINT	• pain when a limb is used or even at rest, not necessarily with a bruise (hematoma) • joint swelling and warmth • child agitated or cries when moving a joint • loss of mobility in a joint, hesitation moving, especially in children	Improperly treated and/or poorly healed bleeding can lead to chronic disorders such as haemophilic arthritis.

COPING WITH THE DIAGNOSIS

Learning you or your child has a bleeding disorder is very upsetting and you may experience a range of different emotions. For some people, it brings fear and anxiety while for others, being able to put a name to symptoms they have lived with for years can be a tremendous relief. Parents may feel guilty to learn their child has an inherited bleeding disorder. All these feelings are normal, and are likely to change over time as you learn more about the condition and the impact it will have on your life. Talking to others: friends, parents, healthcare professionals, and other people with bleeding disorders, can be a great comfort. Learning as much as you can about the disorder will also help you feel more confident and soothe your fears. Get in touch with the Irish Haemophilia Society or your Haemophilia/Bleeding Disorder Treatment Centre to ask questions and discuss options.

HEALTHY LIVING

The recommendations for healthy living are similiar for anyone with or without a coagulation factor deficiency:

- Follow a regular programme of physical activity suited to your lifestyle and capability. Maintaining adequate muscle mass can reduce the risk of bleeds.
- Try to avoid contact sports like boxing, Gaelic football, hurling and rugby to reduce risk of serious injury. The most commonly recommended sports are swimming and cycling.
- Use high quality sports equipment appropriate for any sport (helmet, elbow pads, knee-pads, proper shoes, etc.).
- Eat a well-balanced diet; maintain normal weight.
- Get enough sleep.
- Drink alcohol in moderation only.
- Don't smoke.

PREVENTION

There is no way of fully preventing bleeds but there are a number of things you can do to reduce the likelihood of a bleed occurring:

- Never take aspirin. Aspirin increases the risk of bleeding by inhibiting platelet function.
- Consult your healthcare team before taking any herbal medicinal supplements, vitamins or natural products sold over the counter.
- Take care of your teeth. See the dentist regularly.
- If surgery or any other invasive procedure is necessary, contact your Haemophilia Treatment Centre in advance in case preventative treatment is required.
- If planning a trip, let the Haemophilia Treatment Centre know. They will tell you what precautions to take. Contact details for worldwide Treatment Centres can be found on the Irish Haemophilia Society website: www.haemophilia.ie/treatmentcentresworldwide
- Always stay in touch with the Haemophilia Treatment Centre.

DENTAL CARE

Good oral hygiene is essential to prevent tooth decay and gum disease. For people with bleeding disorders, maintaining good dental health is very important as it reduces the need for dental surgery, which can be complicated by excessive or prolonged bleeding. People with bleeding disorders should:

- Brush teeth at least twice a day
- Floss regularly
- Use a toothpaste containing fluoride
- Get regular checkups

Any type of invasive procedure, such as a tooth extraction or root canal, can cause bleeding in people with bleeding disorders. The dentist should consult with the Haemophilia/Bleeding Disorder Treatment Centre to identify potential risks and properly plan the procedure. Medication may be needed beforehand to help control bleeding and ensure a safe recovery.

MEDICATIONS TO AVOID

Check all medications with your doctor. Some over the counter medications should be avoided because they interfere with clotting. People with bleeding disorders should not take acetylsalicylic acid (ASA or Aspirin®) or nonsteroidal anti-inflammatory drugs (such as ibuprofen and naproxen) without medical advice.

HAVE MEDICAL INFORMATION ON HAND AT ALL TIMES

Carry information about your disorder with you at all times including, the treatment that has been prescribed, the name and telephone number of your physician and contact details for your treatment centre. If you are registered with the National Centre for Hereditary Coagulatuion Disorders (NCHCD) you will receive a 'Bleeding Disorder ID Card' which will give details of your diagnosis and contact information for the centre. This is very useful if attending another hospital. When travelling, find the addresses and telephone numbers of the Haemophilia/Bleeding Disorders Treatment Centres at your destination(s) and bring the information with you.

[Specially printed Travel Cards are available free of charge from the Irish Haemophilia Society.]

SPECIAL ISSUES FOR GIRLS AND WOMEN

Women with clotting factor deficiencies tend to have more symptoms than men because of menstruation and childbirth. Girls may have heavy bleeding when they begin to menstruate. Women with clotting factor deficiencies may have heavier and/or longer menstrual flow, which can cause anaemia (low levels of iron, which results in weakness and fatigue).

Women with clotting factor deficiencies should receive genetic counselling about the risks of having a child well in advance of any planned pregnancies and should see an obstetrician as soon as they suspect they are pregnant. The obstetrician should work closely with the staff of the Haemophilia/Bleeding Disorder

Treatment Centre in order to provide the best care during pregnancy and childbirth and to minimise the potential complications for both the mother and the newborn.

Women with certain factor deficiencies (such as Factor XIII deficiency and afibrinogenemia) may be at greater risk of miscarriage and placental abruption (a premature separation of the placenta from the uterus that disrupts the flow of blood and oxygen to the foetus). Therefore, these women require treatment throughout the pregnancy to prevent these complications. The main risk related to pregnancy is postpartum haemorrhage.

All bleeding disorders are associated with a greater risk of increased bleeding after delivery. The risk and the severity of the bleeding can be reduced with appropriate treatment. This treatment is different for each woman and depends on her personal and family history of bleeding symptoms, the severity of the factor deficiency, and the mode of delivery. Factor replacement may be necessary in some cases.

[For more information on this please see our publication "Women and Bleeding Disorders]

COMPREHENSIVE TREATMENT CENTRES IN IRELAND

DUBLIN

NATIONAL CENTRE FOR HEREDITARY COAGULATION DISORDERS (NCHCD)
ST. JAMES'S HOSPITAL,
JAMES'S STREET,
DUBLIN 8.
TEL: 01 4162141 / 01 4162142

OUR LADY'S CHILDREN'S HOSPITAL CRUMLIN,
CRUMLIN,
DUBLIN 12.
TEL: 01 409 6100

CORK

CORK UNIVERSITY HOSPITAL,
WILTON,
CORK.
TEL: 021 4546400

OTHER TREATMENT CENTRES

UNIVERSITY COLLEGE HOSPITAL, GALWAY
TEL: 091 524 222

LIMERICK REGIONAL HOSPITAL
TEL: 061 482219

WATERFORD REGIONAL HOSPITAL
TEL: 051 848000

CONCLUSION

The rare bleeding disorders described in this booklet affect more than 440 people in Ireland. Information on treatment and diagnosis can be obtained from the National Centre for Hereditary Coagulation Disorders (NCHCD).

The Irish Haemophilia Society represents people with haemophilia, von Willebrands disease and rare bleeding disorders. We encourage you to contact the Irish Haemophilia Society if you require information, advice, support or assistance. Further information is available on our website:
www.haemophilia.ie

[On the following 2 pages you will find tables which illustrate the 'Characteristics of Rare Clotting Factor Deficiencies' and the 'Bleeding Symptoms of Rare Clotting Factor Deficiencies'. We hope this booklet is of assistance to you in understanding Rare Bleeding Disorders.]

Table 1: Characteristics of Rare Clotting Factor Deficiencies

MISSING FACTOR	INCIDENCE*	INHERITANCE	SEVERITY OF BLEEDING	TREATMENT
Factor I Afibrogenemia Hypofibrogenemia Dysfibrogenemia	 5 in 10 million not available 1 in 1 million	 Autosomal recessive Recessive or dominant Recessive or dominant	Usually mild, except in afibrinogenemia	Fibrinogen concentrate Cryoprecipitate Fresh frozen plasma
Factor II	1 in 2 million	Autosomal recessive***	Usually mild	Prothrombin complex concentrate Fresh frozen plasma
Factor V	1 in 1 million	Autosomal recessive	Usually mild	Fresh frozen plasma
Combined factor V and factor VIII	1 in 1 million†	Autosomal recessive‡	Usually mild	Fresh frozen plasma Factor VIII concentrate Desmopressin
Factor VII	1 in 500,000	Autosomal recessive***	Severe when factor levels are low	Recombinant factor VIIa concentrate Factor VII concentrate Prothrombin complex concentrate Fresh frozen plasma
Factor X	1 in 1 million	Autosomal recessive	Moderate to severe when factor levels are low	Prothrombin complex concentrate Fresh frozen plasma
Combined deficiency of vitamin K-dependent clotting factors	not available	Autosomal recessive***	Usually mild, but a few families have reported very low levels and more severe symptoms	Vitamin K Prothrombin complex concentrate Fresh frozen plasma
Factor XI	1 in 100,000	Recessive or dominant	Mild to moderate when factor levels are low	Factor XI concentrate Antifibrinolytic drugs Fibrin glue Fresh frozen plasma
Factor XIII	1 in 3 million	Autosomal recessive	Severe	Factor XIII concentrate Cryoprecipitate Fresh frozen plasma

* Estimates only

*** Can also be acquired later in life because of another medical condition, certain medications, etc.

† 1 in 100,000 in some populations, including Israel, Iran, and Italy

‡ Very rarely, factor VIII deficiency can be inherited separately from only one parent

Table 2: Bleeding Symptoms of Rare Clotting Factor Deficiencies[1]

SYMPTOM	FACTOR I	FACTOR II	FACTOR V	FACTORS V+VIII	FACTOR VII	FACTOR X	FACTOR XI	FACTOR XIII
Nosebleed	Common	Common	Common	Occasional	Common	Common	Common	Common
Easy bruising	Common	Not Available	Common	Common	Common	Common	Common	Common
Heavy or prolonged menstrual bleeding	Common	Common	Common	Common	Common	Occasional	Common	Occasional
Blood in urine	Absent	Rare	Absent	Absent	Rare	Occasional	Absent	Occasional
GI bleeding	Occasional	Occasional	Occasional	Absent	Occasional	Common	Occasional	Occasional
Joint bleeding	Common	Common	Rare	Rare	Occasional	Common	Common	Common
Muscle bleeds	Common	Common	Occasional	Occasional	Occasional	Common	Rare	Occasional
Umbilical cord bleeding	Common	Occasional	Absent	Absent	Rare	Common	Absent	Common
CNS bleeding	Occasional	Rare	Rare	Absent	Occasional	Occasional	Absent	Common
Bleeding from mouth/gums	Common	Common	Common	Common	Common	Common	Occasional	Common
Bleeding during pregnancy/childbirth*	Absent	Not Available	Absent	Absent	Occasional	Absent ‡	Absent	Absent ‡
Major surgery*⁇	Occasional	Occasional	Occasional	Common	Occasional	Common	Common	Absent
Minor surgery⁇	Common	Occasional	Occasional	Common	Common	Common	Common	Common
Other	Rare	Not Available	Rare	Occasional	Absent	Occasional	Rare	Absent

* treatment could not be ruled out

⁇ percentages were calculated on the basis of the number of procedures

‡ percentage was calculated based on one patient

Patients reported absence of this symptom

Rare **0 - 10% patients**
Occasional **10 - 30% patients**
Common **>30% of patients**

1: 100,000 to 1: 3million

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