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NORMAL AND ABNORMAL BLOOD COAGULATION: A SYSTEMATIC REVIEW

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Abstract

The coagulation route is a series of actions that ultimately result in the formation of hemostasis. The intricate process enables quick healing while also helping to avoid bleeding that could otherwise occur on its own. Both the intrinsic and extrinsic routes, which lead to fibrin activation, begin in different places but converge at the same site to produce the same result. The purpose of this procedure is to use a fibrin mesh to help stabilize the ends of the platelets. The mechanism of blood coagulation, which is responsible for maintaining hemostasis, is an intricate process that is carried out by a number of clotting factors. The components I, II, IX, X, XI, and XII are the ones that make up the intrinsic route. Fibrinogen, prothrombin, the Christmas factor, the StuartPrower factor, plasma thromboplastin, and the Hageman factor each have their own names. The variables I, II, VII, and X are the ones that make up the extrinsic route. The factor known as the stable factor is factor VII. The following elements make up the general pathway: I, II, V, VIII, and X. These components, in the form of zymogens, travel through the bloodstream, where they are eventually converted into serine proteases. The process of blood clotting is known as coagulation, and it requires and involves many different components and routes. Disorders that manifest in the organs or components that are essential to the coagulation process can be the root cause of coagulation issues.

Keyword: *Blood Coagulation; Fibrinogen; Hemostasis; Thrombocyte*

INTRODUCTION

The coagulation pathway is a cascade of events leading to hemostasis. The complicated pathway allows for rapid healing and prevention of spontaneous bleeding.

The two pathways, intrinsic and extrinsic, originate separately but converge at a specific point, leading to fibrin activation. The goal is to stabilize the ends of the platelets with a fibrin mesh.[1,2] The function of the coagulation pathway is to maintain hemostasis which is a blockage of bleeding.[3]

Primary hemostasis is the aggregation of platelets that form a plug at the site of damaged endothelial cells. Secondary hemostasis includes two main coagulation pathways, namely intrinsic and extrinsic which meet at one point to form a common pathway. The common pathway ultimately activates fibrinogen to become fibrin. These fibrin subunits have an affinity for each other and combine to form fibrin strands that bind platelets together, stabilizing the platelet plug.[4]

The coagulation mechanism that enables hemostasis is a complex process that is carried out through a series of clotting factors. The intrinsic pathway consists of factors I, II, IX, X, XI, and XII. Each is named, fibrinogen, prothrombin, Christmas factor, StuartPrower factor, plasma thromboplastin, and Hageman factor. The extrinsic pathway consists of factors I, II, VII, and X. Factor VII is called the stable factor. The general pathway consists of factors I, II, V, VIII, X. These factors circulate through the bloodstream as zymogens and are activated into serine proteases.[5,6]

This serine protein works as a catalyst to convert the following zymogen into even more serine proteins, and it is ultimately responsible for activating fibrinogen. These factors are serine proteases: factor II, VII, IX, X, XI, and XII. These enzymes, known as factors V, VIII, and XIII, are not serine proteases. The endothelial collagen that is exposed is what activates the intrinsic pathway, whereas the tissue factors that are generated by endothelial cells in response to injury from the outside world are what activate the extrinsic pathway.[5,6] We compiled this article to assess normal and abnormal coagulation.

METHODS

The author complied with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure that this research was conducted in compliance with the standards cited. This is done to assure the accuracy of the outcomes of this inquiry. This literature review aims to address normal and abnormal coagulation by evaluating or analyzing existing studies on the subject. This article was created with the theme to show significant problems in the issues raised.

We used "normal", "abnormal", and "coagulation" as keywords.The search for studies to be included in the systematic review was carried out from February, 17th 2023 using the PubMed and SagePub databases by inputting the words:

(("microbiologic"[All Fields] OR "microbiologically"[All Fields] OR "microbiology"[MeSH Terms] OR "microbiology"[All Fields] OR "microbiological"[All Fields]) AND ("characterisation"[All Fields] OR "characterisations"[All Fields] OR "characterise"[All Fields] OR "characterised"[All Fields] OR "characterises"[All Fields] OR "characterising"[All Fields] OR "characterization"[All Fields] OR "characterizations"[All Fields] OR "characterize"[All Fields] OR "characterized"[All Fields] OR "characterizes"[All Fields] OR "characterizing"[All Fields]) AND "KPCProducing"[All Fields] AND ("klebsiella pneumoniae"[MeSH Terms] OR ("klebsiella"[All Fields] AND "pneumoniae"[All Fields]) OR "klebsiella pneumoniae"[All Fields])) AND ((y_10[Filter]) AND (ffrft[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])) used in searching the literature.

After reading the research abstract and title, the writers evaluated the studies to determine whether or not they satisfied the inclusion criteria. The writers then choose a number of previous studies to cite as references for this one. After looking at multiple different research that all followed the same pattern, we have arrived at this conclusion. All of the included studies need to be written in English and can't have a publication date earlier than 2013.

In the systematic review, we only looked at studies that qualified to be included if they satisfied all of the inclusion criteria. This restricts the search to only material that is relevant. We do not consider any research results that do not adhere to the criteria we have outlined. After this step comes the evaluation of the research in its entirety. Throughout the course of the investigation of this study, the following information was discovered: names, authors, publication date, location, study activities, and parameters.

Before picking which publications to study further, each author conducted their own independent analysis of the individual studies provided in the publication's title and abstract. Thereafter, we will evaluate all papers that match the inclusion criteria and are acceptable for the systematic review. Then, we will pick which publications to include in the review depending on our findings. This criterion is used to select reviewable manuscripts. to simplify as much as possible the procedure of picking papers for review. Which prior studies were undertaken, and what aspects of those research qualify them for inclusion in the review?

RESULT AND DISCUSSION

Hemostasis comes from the words haima (blood) and stasis (stop) as a process that is very complex and ongoing in preventing spontaneous blood loss and stopping bleeding due to damage to the vascular system. This process includes

blood clotting (coagulation) and involves blood vessels, platelet aggregation (platelet) and plasma proteins both causing clots and dissolving clots.[5,7] Initial vasoconstriction of the wounded blood artery is a hallmark of primary hemostasis. This vasoconstriction causes a reduction in blood flow distal to the site of injury. An early response to injury is vasoconstriction, which is then followed by platelet adhesion to the collagen in the vessel wall that has been exposed to injury and is mediated by von Willbrand factor.[8]

Activated platelets cause the platelet Gp IIb/IIIa receptors to be ready to accept fibrinogen ligands and platelet aggregation occurs and forms a platelet plaque that closes the wound/trauma. This process is then followed by a secondary hemostasis process characterized by activation of coagulation through the intrinsic and extrinsic pathways.[8] Coagulation also known as coagulation is the process by which blood changes from a liquid to a gel which will form a blood clot. This process has the potential to result in hemostasis, the cessation of blood loss from damaged blood vessels, followed by repair.[9] The mechanism of coagulation involves activation, adhesion and aggregation of platelets, and deposition and maturation of fibrin. The mechanism of blood coagulation is complex. This mechanism is initiated when there is trauma to the vessel wall and adjacent tissues, to the blood, or the blood comes in contact with damaged endothelial cells or with collagen or other tissue elements outside the vascular endothelial cells. This mechanism leads to the formation of prothrombin activator which converts prothrombin to thrombin and initiates all the subsequent steps.[8]

The mechanism of clotting generally occurs through three main steps, including: in response to rupture of blood vessels that are damaged, a series of complex chemical reactions occur in the blood involving more than a dozen blood clotting factors. The end result is the formation of a complex of activated substances called prothrombin activator; prothrombin activator catalyzes the conversion of prothrombin to thrombin; and thrombin acts as an enzyme to convert fibrinogen into fibrin threads that string together platelets, blood cells, and plasma to form a clot.[10]

Table 1. Blood clotting factors [5,6]

Factor	Name	Fuction / Role
I	Fibrinogen	Fibrin precursor (polymerized protein) or in other words is a protein-breaking enzyme (serine protease) which is useful for the next procoagulant activation.
II	Prothrombin	Precursor to the proteolytic enzyme thrombin and possibly another accelerator of prothrombin conversion
III	Thromboplastin	Tissue lipoprotein activator on prothrombin
IV	Calcium	Required for prothrombin activation and fibrin formation
V	Proaccelerin/accelerator plasma globulin	Plasma factor that accelerates the conversion of prothrombin to thrombin
VII	Proconvertine; serum prothrombinogen; convertin/accelera prothrombin tor	Serum factors that accelerate the conversion of prothrombin
VIII	Antihemophilic factor A (factor IIR- von Willebrand) / hemophilic globulin	Plasma factor associated with platelet factor III and Christmas factor IX; activate prothrombin
IX	Antihemophilic factor B; Christmas factor; platelet cofactor II	Serum factor related to platelet factors III and VIIIAHG ; activate prothrombin
X	Stuart-Prower factor; prothrombinase	Plasma and serum factors that act as prothrombin conversion accelerators
XI	Anteseden tromboplastin plasma (ATP)	Plasma factor activated by Hageman factor (XII) which acts as an accelerator of thrombin formation
XII	Hageman Factor; glass factor	Plasma factor that activates factor XI (ATP)
XIII	Fibrin-stabilizing factor; the MaleLorand factor	A plasma factor that produces a stronger fibrin clot that is insoluble in urea
-	Fletcher factor (Prakalikrein)	Contact activating factor
-	Fitzgerald factor (a large molecular weight quininogen) Platelets	Contact activating factor

Normal Coagulation

Clotting factors present in the blood are a series of numbers and Roman numerals, depending on which one is identified first. This factor will be arranged in the letter "a" which indicates that the factor is active.[5,6,10] One of the organs involved in the coagulation process is the liver. The liver is responsible for the formation of factors I, II, V, VII, VIII, IX, X, XI, XIII, and proteins C and S. Factor VII is made by the vascular endothelium. Liver abnormalities can lead to a lack of

coagulation factors and lead to bleeding. As soon as a vessel is cut or ruptured, the damaged vessel wall itself causes the smooth muscle of the vessel wall to contract, so that immediately the blood flow from the ruptured vessel is reduced.[2,11]

Contraction occurs as a result of: local myogenic spasm, local autacoid factors derived from traumatized tissue and blood platelets, and various nervous reflexes. The more severe the damage, the more intense the spasm will be. This local spasm of vessels can last minutes or even hours, during which time the process of platelet plug formation and blood clotting takes place.[5,6] Platelets are responsible for repairing damaged blood arteries thanks to a number of crucial tasks that platelets do on their own.[11] Platelets undergo a rapid and dramatic transformation in their characteristics whenever they come into touch with the damaged surfaces of blood vessels, and more specifically with the collagen fibers that are found in the walls of blood vessels.[5,6]

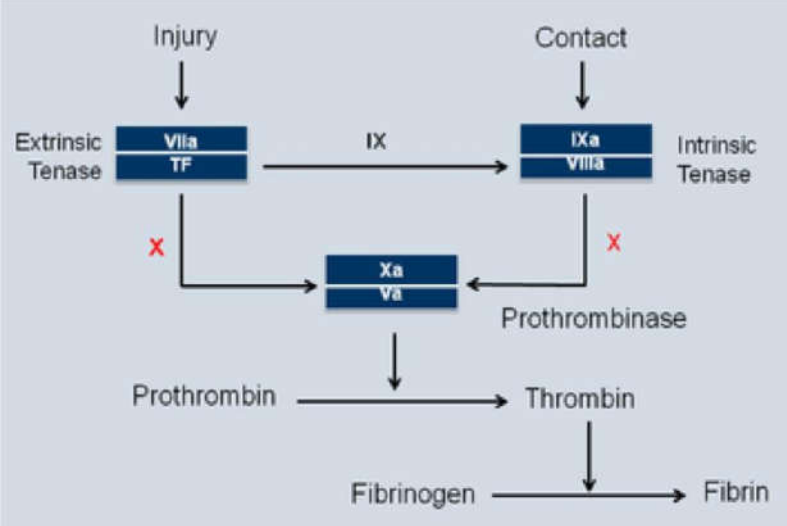

Figure 1. Formation of the coagulation cascade[12]

Platelets begin to swell, become irregular in shape with protrusions protruding from their surface. The contractile proteins contract forcefully and cause the release of granules which contain various active factors so that the platelets become sticky and adhere to collagen in the tissues and to a protein called von Willebrand factor which leaks from the plasma into the traumatized tissue. Platelets secrete large amounts of ADP (adenocyte diphosphate) and their enzymes form thromboxane. ADP and thromboxane then activate adjacent platelets, and because of the stickiness of these additional platelets, they adhere to the original activated platelets.[5,6,13]

The third mechanism is the formation of blood clots. Clots begin to form within 15-20 seconds if the trauma to the vessel wall is severe, and within 1-2 minutes if the trauma is minor.[11] Activator substances from damaged blood vessel walls, from platelets, and from blood proteins attached to damaged blood vessel walls, will initiate the blood clotting process. All parts of the injured vessel or the open end of the vessel will be filled with a blood clot. After 20 minutes to an hour, the clot will retract. This will close the wound site. Platelets also play an important role in this clot retraction event.[5,6,13] The injured tissue releases several factors called tissue factor or tissue thromboplastin. This factor is composed primarily of phospholipids from tissue membranes plus lipoprotein complexes that function primarily as proteolytic enzymes. The lipoprotein complex of tissue factor then combines with factor VII and, in the presence of calcium ions, this factor acts as an enzyme on factor X to form activated factor X (Xa). Activated factor X binds immediately to tissue phospholipids that are part of tissue factor, or to additional phospholipids released from platelets, including factor V, to form a compound called prothrombin activator. Within a few seconds, in the presence of calcium ions, they break down prothrombin into thrombin, and the coagulation process takes place.[5,6,13]

Initially, factor V contained in the prothrombin activator complex is inactivated, but once the clotting process begins and thrombin begins to form, the proteolytic action of thrombin activates factor V. This factor then becomes a powerful additional accelerator of final prothrombin activation, Factor X. it is activated (Xa) that is the actual protease that causes the breakdown of prothrombin to form thrombin. Activated Factor V (Va) greatly accelerates the action of this protease, while platelet phospholipids act as a transport vehicle accelerating the process.[5,6,13]

The second mechanism for the initiation of prothrombin activator formation, and thus the initiation of the formation process, begins with trauma to the blood itself or blood in contact with collagen in the damaged vessel wall. Trauma to the blood or blood contact with blood vessel wall collagen will alter two important clotting factors in the blood: factor XII and platelets. When factor XII is disturbed, for example by coming into contact with collagen or with a wet surface such as glass, it transforms into a new molecular form, namely a proteolytic enzyme called “activated factor XII/XIIa”.[14,15]

At the same time, trauma to the blood damages platelets by contact with collagen or a wet surface (or is damaged in other ways), and this releases various platelet phospholipids that contain lipoproteins, called platelet factor 3, which also play

a role in further coagulation process. Activated Factor XII acts enzymatically on Factor XI and also activates it. This is the second step in the intrinsic pathway. This reaction also requires HMW (high molecular weight) quininogen, and is accelerated by prekalirein.[14]

Because Factor XI is activated. Activated Factor XI acts enzymatically on Factor IX and activates it. Activated factor IX, which cooperates with activated factor VIII and with platelet phospholipids and factor 3 from damaged platelets, activates factor X. This step in the intrinsic pathway is basically the same as the last step in the extrinsic pathway. That is, activated factor X combines with factor V and platelet or tissue phospholipids to form a complex called prothrombin activator. The prothrombin activator within seconds initiates the breakdown of prothrombin into thrombin, and thus the subsequent coagulation process can take place.[16]

The conversion of prothrombin to thrombin can occur in the following ways: 1) prothrombin activator is formed as a result of ruptured blood vessels or as a result of damage to special substances in the blood; 2) prothrombin activator in the presence of sufficient Ca++ ions will cause the conversion of prothrombin to thrombin; and 3) thrombin causes polymerization of fibrinogen molecules into fibrin fibers within another 10 to 15 seconds.[16]

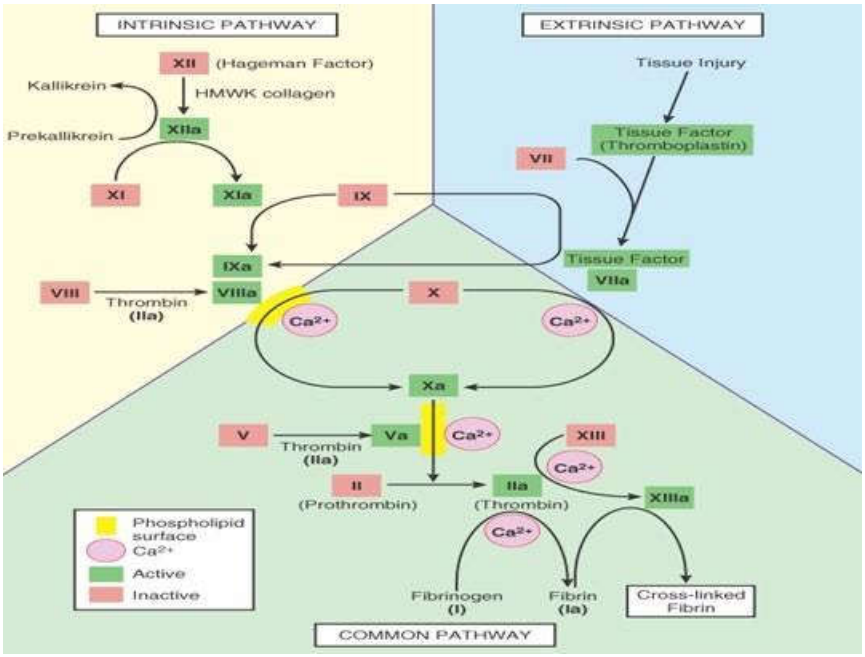

Figure 2. Schematic of co-pathways of blood clots [5,7]

The factor that limits the rate of blood clotting is usually the formation of the prothrombin activator and not the subsequent reactions, because the final step usually occurs too quickly to form the clot itself. Platelets also play an important role in converting prothrombin to thrombin, because much of the prothrombin first attaches to prothrombin receptors on platelets that have bound to damaged tissue. Factor X activity due to reactions of the extrinsic and intrinsic pathways. The next step in fibrin formation takes place when Kator Xa, assisted by phospholipids from activated platelets, breaks down prothrombin to form thrombin.[16]

Then thrombin breaks down fibrinogen to form fibrin. This fibrin is initially a soluble jelly, is stabilized by factor XIIIa and undergoes polymerization into a network. Fibrinogen is a protein with a large molecular weight (BM = 340,000) which is present in plasma at levels of 100 to 700 mg/dl. Fibrinogen is formed in the liver, and liver disease can reduce circulating fibrinogen levels, as well as prothrombin concentrations. Due to its large molecular size, little fibrinogen normally leaks from the blood vessels into the interstitial fluid, and because fibrinogen is a principal factor in the clotting process, interstitial fluid usually does not clot.[17]

However, when capillary permeability is pathologically increased, fibrinogen will leak into the tissue fluids in sufficient quantities to cause coagulation of these fluids in much the same way that plasma and blood coagulate. Thrombin is a protein enzyme with weak proteolytic ability. It acts on fibrinogen by releasing four low molecular weight peptides from each fibrinogen molecule, thus forming one fibrin monomer molecule which has the automatic ability to polymerize with other fibrin monomer molecules to form fibrin threads.[16]

In this way, within seconds many molecules of fibrin monomer polymerize into long fibrin threads, which are the clotting reticulum. The monomeric fibrin molecules in the early stages of polymerization are held together by weak noncovalent hydrogen bonds, and these newly formed strands are not cross-linked strongly with each other. Therefore, the resulting clot is not strong and easily dispersed. But another process occurs in the next few minutes that greatly strengthens the

fibrin network. This process involves a substance called fibrin stabilizing factor, which is present in small amounts in the normal form of plasma globulin but is also released from platelets trapped in the clot.[16]

Before this fibrin stabilizing factor can act on fibrin threads, it must itself be activated. The same thrombin that causes fibrin formation also activates the fibrin stabilizing factor. This activated substance then acts as an enzyme to cause covalent bonds between more and more fibrin monomer molecules, as well as cross-links between adjacent fibrin fibers, thereby greatly increasing the three-dimensional strength of the fibrin network. A blood clot consists of a network of fibrin threads running in all directions that ensnare blood cells, platelets and plasma.[16]

The fibrin clot also adheres to the surface of the damaged blood vessel to prevent subsequent blood leakage. Once a blood clot has formed, it will expand to the surrounding area. The clot undergoes a chain cycle (positive feedback) to make it easier for the clot to become large. One of the most important reasons for this process is the proteolytic action of thrombin, which allows it to act on clotting factors other than fibrinogen. Thrombin has a direct proteolytic effect on prothrombin itself so that more thrombin is formed, and this acts on several clotting factors that are responsible for the formation of prothrombin activator.[16]

Once a blood clot has formed, two processes occur: the clot can be invaded by fibroblasts, which then form connective tissue throughout the clot and dissolution of the clot. A clot that forms in a small wound in the vessel wall is usually invaded by fibroblasts, which begin several hours after the clot forms. This continues until complete clot formation of fibroblastic tissue occurs in approximately 1 to 2 weeks. On the other hand, when a large amount of blood leaks into a tissue and an unneeded tissue clot occurs, special substances present in the clot itself become activated.[16]

When a clot forms, it contains large amounts of plasminogen along with other plasma proteins. Plasminogen will not become plasmin or cause clot lysis before it is activated. Injured tissue and vascular endothelial cells very slowly release a potent activator; tissue plasminogen activator (t-PA) in the following days after the clot managed to stop the bleeding. Eventually plasminogen converts into plasmin which then removes the unnecessary blood clot.[16]

Abnormal Coagulation

Disorders of the coagulation system, diseases of the platelets, or disorders of the blood vessels can all lead to abnormal bleeding. Coagulation disorders can be acquired or they can be inherited in some cases. By reducing clotting factor production, severe liver disease (cirrhosis, fulminant hepatitis, and acute fatty liver of pregnancy) can disrupt hemostasis. Due to the fact that all coagulation components are produced in the liver, both PT and PTT are lengthened in severe liver diseases. Infrequently, decompensated liver illness also produces increased fibrinolysis and bleeding due to diminished hepatic alpha 2-antiplasmin production.[2,11]

Von Willebrand disease is a prevalent disorder in which the associated factor VIII deficiency is typically insufficient to lengthen the prothrombin time (PTT). Patients with normal initial test results, bleeding symptoms or signs, and a positive family history should be evaluated for von Willebrand disease (VWD) by measuring plasma von Willebrand factor (VWF) antigen, ristocetin cofactor activity (an indirect test for large VWF multimers), VWF multimer pattern, and factor VIII levels.[18]

Hereditary hemorrhagic telangiectasia (also known as Osler-Weber-Rendu Syndrome) is a vascular malformation illness that is inherited. Individuals with this condition have red-to-violet telangiectatic lesions on the cheeks, lips, oral and nasal mucosa, and digit tips. Individuals may endure repeated bleeding from the nasal mucosa and gastrointestinal system, as well as other potentially life-threatening complications, if they have an arteriovenous malformation.[19]

When thrombocytopenia is present, the peripheral blood smear is typically used to determine the etiology of the condition. Patients should be screened for HIV infection even if the smear results come back normal. It is possible that the patient has immune thrombocytopenia (ITP) if the result of the HIV test is negative, the patient is not pregnant, and the patient has not taken any medication that is known to cause platelet destruction. It is possible that the patient has thrombotic thrombocytopenic purpura (TTP) or hemolytic-uremic syndrome (HUS) if the smear reveals symptoms of hemolysis, such as fragmented red blood cells on the smear or a declining hemoglobin level.[20,21]

Patients who have Shiga-like toxin-induced hemorrhagic colitis, which can occur after infections with many Escherichia coli serotypes, are more likely to develop "classic" HUS. Those who were born with congenital defects of the alternative complement pathway have a very small chance of developing a "atypical" form of HUS. The results of the Coombs test for TTP and HUS came back negative. If the complete blood count and peripheral blood smear both show additional cytopenias or aberrant white blood cells, then it is likely that the patient has a hematologic disorder that affects more than one cell type.20,21

After that, a biopsy and an aspiration of the bone marrow are required for the diagnosis. A prolonged PTT in the presence of normal platelets and PT suggests hemophilia A or B. Assays for factors VIII and IX are indicated. Autoantibodies against factor VIII and antibodies against protein-phospholipid complexes are examples of inhibitors that specifically

prolong the PTT (lupus anticoagulant). When a prolonged PTT does not correct after 1:1 mixing with normal plasma, clinicians suspect one of these inhibitors. A prolonged PT with normal platelets and PTT suggests a deficiency of factor VII.[22]

Congenital factor VII deficiency is uncommon; however, because factor VII has a short half-life in plasma, it drops to low levels faster than other vitamin K-dependent coagulation factors in patients starting warfarin anticoagulation or with incipient liver disease. Prolonged PT and PTT with thrombocytopenia are indicators of DIC, particularly in patients with obstetric complications, sepsis, cancer, or shock. Serial testing reveals elevated levels of D-dimer (or fibrin degradation products) and decreasing plasma fibrinogen levels.[22]

CONCLUSION

Coagulation is a blood clotting process that requires and involves many factors and pathways. Disturbances in coagulation can be caused by disorders that occur in organs or factors involved in coagulation.

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