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Elevated factor VIII level: An implication for thrombosis during pregnancy

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Abstract

Hemostasis is the process by which the body maintains the integrity of blood vessels and regulates blood circulation. It involves arresting bleeding, and possibly mending broken or severed blood vessels. It is achieved through a series of steps, including vascular spasm, platelet plug formation, coagulation cascade, and fibrinolysis. Skipping any of these steps causes severe bleeding and death. During pregnancy, the hemostatic system undergoes significant changes to adapt to the physiological demands. These changes aim to prevent excessive bleeding during and after childbirth. Hypercoagulability, characterized by elevated clotting factors and reduced fibrinolytic activity, is common during pregnancy. While these alterations in the coagulation system help prevent postpartum bleeding, they also increase the mother's risk of thrombosis by a factor of five. This hypercoagulable state is caused by pregnancy-related factors like venous stasis, endothelial damage, and hormonal fluctuations. However, studies have shown that an increase in Factor VIII levels poses as a risk factor for both venous and arterial thrombosis. The determination of plasma factor VIII levels is influenced by genetic factors, as well as the levels of von Willebrand factor (VWF) and the individual's blood group. The findings of familial investigations have revealed that the concentration of factor VIII is indeed hereditary, exhibiting a lesser degree of variability among twins when compared with individuals who lack a familial connection. Continuous monitoring should be performed on pregnant patients with thrombosis risk factors. This intervention is implemented with the aim of mitigating the potential aggravation of deep vein thrombosis (DVT) and the subsequent development of post-thrombotic syndrome.

Keywords: Hemostasis; Coagulation cascade; Hypercoagulability; Factor VIII; Thrombosis; Pregnancy

1 Introduction

Hemostasis is a process or mechanism that preserves the integrity of blood vessels and blood flow within the body. It involves the cessation or sluggishness of blood flow, the cessation of bleeding (as by a hemostatic substance), and the likely healing of broken or severed blood vessels. The three steps of the hemostatic process are vascular spasm, platelet plug formation, and coagulation [1]. If any of these steps are skipped, severe bleeding and death are likely to result.

Vasoconstriction involves the involuntary contraction of the smooth musculature situated within the vascular walls. This happens immediately after the vessel walls are slashed.

Similar to larger blood vessels, these muscles exhibit the presence of both circular and longitudinal sections. The circular layers exhibit a tendency for impeding hemodynamic circulation, whereas the longitudinal sections, if present,

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exert a retractile force on the vasculature, causing it to recede into the adjacent tissue. In relation to vessel injury, it is postulated that the release of endothelin (ET -1,2,3) by endothelial cells and nociceptors triggers the vascular spasm response [2]. This particular phenomenon generally exhibits a duration of approximately 30 minutes, although it may persist for extended periods of time depending on the gravity of the injury and the promptness of the body's essential physiological mechanisms in mounting a response.

2 Primary Haemostasis (Platelet Plug development)

During the subsequent phase, platelets, which are suspended within the plasma, come into contact with exposed connective tissue and collagen fibers at the site of an artery rupture. Platelets begin to aggregate, spike, and adhere to the collagen and endothelium linings that have been exposed. This physiological process is effectively facilitated by von Willebrand factor, a crucial component that aids in the stabilization of the recently developed platelet plug [3]. Upon platelet aggregation, a cascade of events is initiated, leading to the release of various bioactive substances into the plasma. These substances, including adenosine diphosphate (ADP), serotonin, prostaglandins, and others, play a crucial role in facilitating the clotting process [4].

- Adenosine diphosphate (ADP) aids platelet aggregation at the site of injury, thereby promoting the enlargement and reinforcement of the platelet plug.
- Serotonin, a chemical that maintains normal blood pressure.
- Prostaglandins and phospholipids, which will be discussed further, help keep blood vessels narrowed and activate additional clotting molecules.

A platelet plug can be used to patch a minor artery tear until the body can implement more extensive and permanent repairs [5].

3 The Coagulation Cascade

The formation of thrombus entails a multifaceted and long-lasting mechanism. This sequence of events is sometimes called a cascade because of the chain reaction they create. Fibrin, an insoluble thread-like protein derived from fibrinogen, a protein found in plasma, undergoes polymerization to generate a meshwork structure that effectively traps platelets and blood cells. In the intricate coagulation cascade, there exist specific entities referred to as clotting/coagulation factors, which initiate a series of intricate events that subsequently activate more of these substances. In most cases, trauma serves as the trigger for the extrinsic pathway, whereas the intrinsic pathway commences within the circulating blood and is initiated by damage to the inner lining of the blood vessels [6].

The formation of the common pathway occurs when these two entities converge. Both calcium ions (Ca2+) and vitamin K, two out of the twelve recognized clotting factors, are essential for the execution of all three hemostatic actions.

3.1 The Extrinsic Pathway

This process begins when there is damage to the tissues around the site of the injury. When damaged extravascular cells come into contact with blood plasma (thromboplastin), they release factor III. The formation of an enzyme complex occurs through the sequential addition of calcium ions (Ca2+) and factor VII, also known as proconvertin [7]. This complex is then activated by factor III. This enzyme complex activates the below-described common pathway by stimulating factor X (Stuart-Prower factor). The peak of the extrinsic pathway occurs swiftly within a few seconds. The response time is shorter and more direct. Another name for the extrinsic pathway is the tissue factor pathway [8].

3.2 Intrinsic Pathway

The extrinsic pathway is shorter and simpler than the intrinsic, or contact activation, pathway. The substances in this pathway play crucial roles in the circulatory system. When factor XII, also known as Hageman factor, encounters exogenous substances, as exemplified by the introduction of a blood specimen into a receptacle composed of glass material, a cascade of events begins that can be set off by tissue damage caused by internal factors like vascular disease. The activation of Factor XII occurs within the human body upon interaction with negatively charged molecules, specifically inorganic polymers and previously generated phosphate during the sequence of reactions along the intrinsic pathway [9]. The initiation of factor XI (also known as antihemolytic factor C) by factor XII results in the subsequent initiation of factor IX. The activation reactions become faster by the release of substances by platelets.

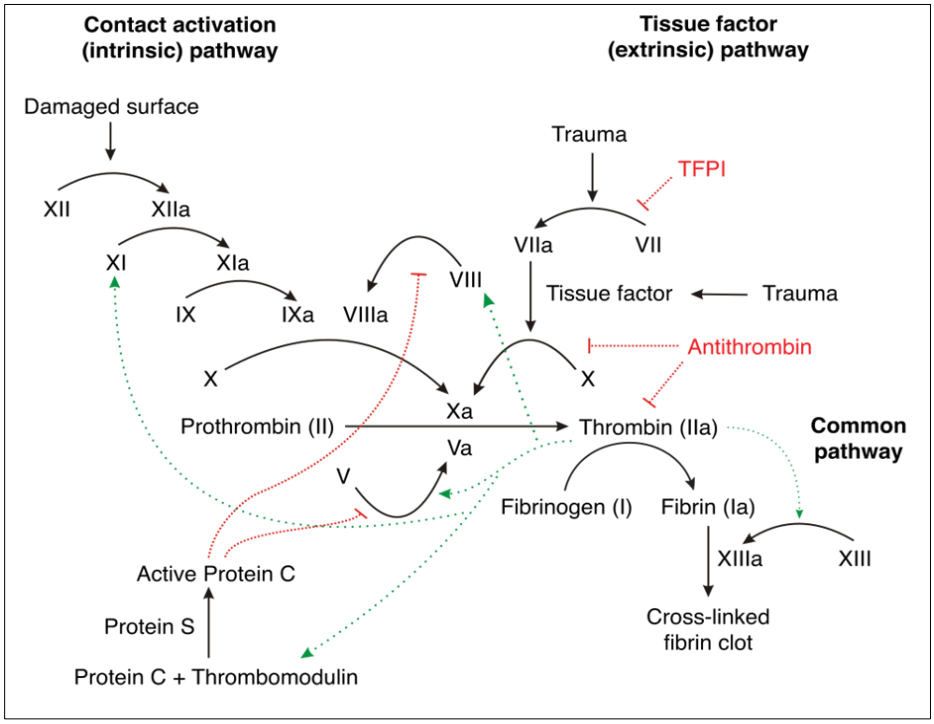
In the context of hemostasis, it is noteworthy that platelets and endothelial cells collaborate in the formation of an enzyme complex consisting of factor VIII (also known as antihemolytic factor A) and factor IX (commonly referred to as plasma thromboplasmin) [10]. This intricate complex serves the purpose of activating factor X (alternatively known as Stuart-Prower factor or thrombokinase), thereby initiating the common pathway. Within a short period of time, the series of occurrences pertaining to the intrinsic pathway wraps up.

3.3 Common Route

The common pathway, responsible for the formation of fibrin to occlude the vessel, is initiated by both the intrinsic and extrinsic pathways [11]. Following activation of factor X via either the intrinsic or extrinsic pathway, the inactive enzyme prothrombin is converted into the active enzyme thrombin by the enzyme prothrombinase. Thrombin then converts soluble fibrinogen into fibrin protein strands. Factor XIII subsequently contributes to the stabilization of the fibrin clot.

3.4 Fibrinolysis

During the recovery of the blood vessel, it becomes necessary to dissolve the clot in order to restore normal blood flow. Fibrinolysis is the physiological process by which a clot undergoes degradation over time [12]. Platelet proteins involved in contractility play a role in influencing clot stability. The contraction of these proteins generates tension, leading to the fusion of the clot's edges as the clot forms. The intricate cascade of reactions involving factor XII and protein-catabolizing enzymes displays a considerable degree of complexity. Fibrin degradation occurs when the inert protein plasminogen is converted into the dynamic protein plasmin [13]. Furthermore, the vasodilator known as bradykinin is released, effectively counteracting the physiological impact caused by the serotonin and prostaglandins released by the platelets. Consequently, the smooth musculature enveloping the arteries and veins relaxes, thereby facilitating the restoration of blood circulation.



Source: https://teachmephysiology.com/immune-system/haematology/coagulation/

Figure 1 The Coagulation Cascade

4 Clotting Factors

The liver and thrombocytes are responsible for the secretion of the predominant portion of coagulation factors within the human body. Vitamin K, which is fat-soluble, is required for their production in the liver. Vitamin K, similar to biotin and folate, possesses a unique attribute in that it is acquired not only through dietary means but also synthesized endogenously by commensal bacteria residing within the large intestine. Calcium ion, also known as factor IV, is

acquired via dietary intake and the process of bone breakdown. Recent findings indicate that distinct receptor sites located on the surface of platelets are responsible for the activation of various clotting factors [14].

The clotting factors are 12 in number and are sequentially designated from I to XIII based on their chronological discovery with an omission of factor VI [15]. Initially it was believed to be a separate coagulation factor, however, it is presently recognized as being indistinguishable from factor V, hence, instead of renumbering the remaining factors, factor VI was intentionally retained as a temporary marker and a means of remembering the progressive nature of medical knowledge.

Table 1 Coagulation Factors

***Vitamin K required.**				
Clotting Factors				
Factor number	**Name**	**Type of molecule**	**Source**	**Pathway(s)**
I	Fibrinogen	Plasma protein	Liver	Common, converted into fibrin
II	Prothrombin	Plasma protein	Liver*	Common, converted into thrombin
III	Tissue thromboplastin or tissue factor	Lipoprotein mixture	Damaged cells and platelets	Extrinsic
IV	Calcium ions	Inorganic ions in plasma	Diet, platelets, bone matrix	Entire process
V	Proaccelerin	Plasma protein	Liver, platelets	Extrinsic and intrinsic
VI	Not used	Not used	Not used	Not used
VII	Proconvertin	Plasma protein	Liver *	Extrinsic
VIII	Antihemolytic factor A	Plasma protein factor	Platelets and endothelial cells	Intrinsic, deficiency results in hemophilia A
IX	Antihemolytic factor B (plasma thromboplastin component)	Plasma protein	Liver*	Intrinsic, deficiency results in hemophilia B
X	Stuart–Prower factor (thrombokinase)	Protein	Liver*	Extrinsic and intrinsic
XI	Antihemolytic factor C (plasma thromboplastin antecedent)	Plasma protein	Liver	Intrinsic, deficiency results in hemophilia C
XII	Hageman factor	Plasma protein	Liver	Intrinsic, initiates clotting in vitro also activates plasmin
XIII	Fibrin-stabilizing factor	Plasma protein	Liver, platelets	Stabilizes fibrin, slows fibrinolysis

5 Hemostasis in Pregnancy

Hemostasis undergoes significant modifications throughout a typical pregnancy. These modifications help preserve placental function and prevent excessive bleeding. The majority of the modifications in coagulation result in hypercoagulability, which protects the mother from excessive bleeding after delivery or miscarriage [16]. Hypercoagulability, endothelial damage, and venous stasis all contribute to the prothrombotic state that is pregnancy [17]. This hypercoagulable state is the most important predictor of thrombosis during pregnancy. The most commonly reported hemostatic disorder in otherwise healthy women is thrombocytopenia [18]. This is partially due to the effects of hemodilution, but increases in mean platelet volume show that there is also compensated platelet destruction.

During pregnancy, fibrinolytic activity is lowered and remains low during labour and delivery due to decrease in t-PA activity [19]. t-PA activity remains low until one hour postpartum and then rebounds to normal. Blood coagulation and fibrinolysis appear to restore to normal levels three weeks after delivery.

5.1 Coagulation System

During a normal pregnancy, factors VII, VIII, IX, X, XII, VWF, and fibrinogen increases significantly, whereas factors II and V remain largely unchanged [20]. All of these modifications are physiological preparations for the hemostatic challenge of childbirth. Increased indicators of hemostatic activity, including prothrombin fragment F1+2 and D-dimer, demonstrate this hemostatic activation. Protein C and antithrombin are unaltered, although Protein S appears to decrease, however, it is unknown if this decrease contributes to the hypercoagulability of pregnancy.

The risk of thrombosis is heightened by factor VIII, with a more notable impact on venous thrombosis compared to arterial thrombosis [21]. The likelihood of developing venous thrombosis escalates as factor VIII levels rise. Specifically, factor VIII levels of 150 IU/dL are linked to 16% of venous thrombotic events, whereas only 4% of arterial thrombosis events are associated with this factor VIII level [22]. The increased levels of factor VIII in an individual's system can potentially increase the likelihood of venous thrombosis due to its capacity to enhance thrombin production and/or induce acquired APC resistance [23]. The elevated production of thrombin and the adherence/aggregation of platelets triggered by VWF at sites of arterial wall damage could potentially explain the correlation observed between factor VIII and arterial thrombosis. While anyone can develop a blood clot that could cause a venous thromboembolism (VTE), the risk is five times higher for pregnant women [24].

Pregnancy, childbirth, and the first three months after giving birth are times when women are especially at risk for developing blood clots [25]. This may occur as a result of an accident, immobilization (like bed rest or recovery from delivery), pregnancy (increased procoagulant activity during pregnancy, reduced blood circulation to the lower extremities later in pregnancy as a result of compression of the blood vessels around the pelvis by the growing baby), complications during labor and delivery (such as a C-section), or surgery. Additional factors such as a personal or family history of blood clots or a blood clotting abnormaly, as well as certain chronic medical conditions, such as heart or lung diseases, diabetes, and infection should be considered. Tissue damage, clotting, and changes in blood composition can result from any of these factors. The predominant genetic predisposing factors for venous thrombosis include alterations in the procoagulant and anticoagulant pathways, which collectively contribute significantly to the occurrence of thrombotic events. Deep vein thrombosis (DVT) exhibits a prevalence up to fivefold higher in gravid females compared to their non-gravid counterparts [26].

In countries with low health care infrastructure, hemorrhage stands as the foremost etiology contributing to maternal mortality [27]. However, it is important to note that embolic illness is the primary cause of maternal mortality in both the United States and other developed nations [28]. All three trimesters have a similar risk of thrombosis, but the risk rises in the first six weeks after giving birth [29]. Post-thrombotic syndrome (PTS) is associated not only with mortality and acute morbidity, but also with chronic impairment. Most pregnant women with deep vein thrombosis (DVT) develop serious complications, such as edema, skin abnormalities, and even recurrent thrombosis and ulceration.

The potential for arterial thrombosis in individuals with coronary heart disease and stroke may be heightened due to an elevated factor VIII level, a recognized risk factor for venous thrombosis. Due to hormonal changes, venous tone decreases, and the uterus grows, blocking veins and causing venous stasis. Between 25 and 29 weeks of pregnancy, venous flow velocity in the legs decreases by around 50% [30]. Normal venous velocities typically return between weeks 6 and 8 postpartum [31]. 82% of pregnant and postpartum women with DVT have it in their left lower extremity [32]. Possible anatomical causes could be the presence of the right common iliac artery exerting pressure on the left common iliac vein has been observed, which is made worse by the expanding uterus [33].

6 Determinants of Plasma Factor VIII Level

According to family studies conducted on healthy individuals, hereditary variables have been shown to affect the concentration of factor VIII [34]. The plasma's factor VIII concentration can be forecast based on the variables of von Willebrand factor (VWF) and blood group [35]. Blood type and endothelial stimulation are known to affect factor VIII levels. However, note that a significant portion of factor VIII is found in circulation as a complex with von Willebrand factor (VWF).

When compared to blood group O, non-O blood groups (A, B, AB) had higher levels of vWF and factor VIII, with a mean difference of 31.5 IU/dL for vWF:Ag and 22.4 IU/dL for factor VIII:Ag, respectively [36]. Extremely high levels of vWF

are found in people with blood group AB, while moderate levels are found in people with blood groups AA, AO, BB, and BO [37]. Blood type affects factor VIII concentration primarily through vWF's mediating effect.

The half-life of infused factor VIII demonstrated a notable decrease in patients possessing blood group O (15.3 hours) in comparison to individuals with blood group A (19.7 hours) [38]. Individuals of the same ABO blood group and plasma vWF concentration can be predicted to have the same half-life for factor VIII.

It has been observed that only 50% of cases with consistently elevated factor VIII levels exhibit concurrent high vWF:Ag levels, indicating that vWF is not invariably accountable for the occurrence of elevated factor VIII plasma levels [39]. As of yet, no variants in the factor VIII or vWF genes have been linked to increased factor VIII levels. There were no sequence changes in either the promoter or the 3'-terminus of the factor VIII gene in 62 patients with thrombosis and elevated factor VIII levels. Females have higher factor VIII levels than males, and African Americans have higher factor VIII levels than whites [40].

6.1 Other Factors That Affect Plasma Factor VIII Concentrations

BMI, glucose (diabetes mellitus), insulin, fibrinogen, and triglyceride levels are positively correlated with Factor VIII levels, as reported by Kamphuisen et al. [40]. The use of oral contraceptives does not appear to affect factor VIII concentrations.

According to research by Jacobsen, A. F. et al. elevated factor VIII levels can be the result of exposure to multiple stressors [28]. Temporary increases in factor VIII are produced during exercise, most likely due to the activation of adrenaline and 2-adrenoreceptors. Both 8-arginine vasopressin and its analogue, 1-deamino-8-D-arginine vasopressin, elevate plasma levels of vWF and factor VIII by signaling via the V2 receptor. Factor VIII levels tend to rise steadily in response to a variety of medical conditions, including pregnancy, surgery, chronic inflammation, cancer, liver illness, hyperthyroidism, intravascular hemolysis, and renal disease [41]. In the vast majority of cases, there is a concurrent increase observed in the levels of Factor VIII and von Willebrand factor antigen (vWF:Ag).

7 Treatment and Clinical Outcomes

Once diagnosed, patients with abnormally high factor VIII levels should undergo constant monitoring due to the increased risk of DVT aggravation. Both pulmonary embolism and post-thrombotic syndrome can be mitigated through proactive measures. An incapacitating long-term effect of proximal DVT is post-thrombotic syndrome, with degrees ranging from moderate to severe. Inadequate recanalization and/or persistent damage to the venous valves are responsible for valvular reflux, as stated by Galanaud, J. P., and Kahn, S. R. [42, 43]. Its mechanism is unclear, but tiredness, pain, swelling, and edema in the legs are common clinical presentations. In severe cases of PTS, venous ulcers can develop [43]. Berg et al. found that 7% of pregnant women with severe PTS had DVT in their lower extremities, and that 42% of pregnant women with DVT in their lower extremities had PTS [44].

8 Use of therapy

The first line of defense against DVT is medical management. Low molecular weight heparins (LMWH) is the drug of choice for therapy, just as it is for prophylaxis, and can be taken at full therapeutic dose or titrated to achieve therapeutic efficacy [45].

9 Exposure to Radiation

The pregnant patient poses a challenging management issue. Based on the administered radiation dosage and the developmental stage of the embryo, there can be a variety of effects on the developing fetus from IVC filter implantation and catheter-directed thrombolysis (CDT). According to the pronouncement made by the esteemed International Commission on Radiological Protection, it has been duly noted that exposures below the threshold of 100 mGy are not anticipated to induce any deterministic effects of practical significance in the context of embryonic and fetal development [46].

10 Use of IVC Filters

Preventing pulmonary embolism while pregnant is possible with the help of IVC filters. But in pregnant women with DVT there isn't much proof to back up their regular use. There is a lack of information about using IVC filters while pregnant. IVC perforations, filter fractures, migrations, and lost temporary devices have all been reported [47].

However, while the Society of Interventional Radiology (SIR) does recognize absolute and relative criteria for IVC filter installation, there are no separate indications for pregnant women. In light of the administration of anticoagulant medication and the potential complications that may arise, such as heparin-induced thrombocytopenia (HIT), allergic reactions to heparin, excessive bleeding, or contraindications to anticoagulation following recent neurosurgical interventions, it is noteworthy that a significant number of inferior vena cava (IVC) filters were inserted during pregnancy due to absolute indications of unsuccessful medical treatment for venous thromboembolism (VTE) [48]. Indicators such as unstable, floating, or very large DVTs, or thrombus spreading into the IVC, should be closely monitored in the weeks leading up to delivery. The review also found that filters were successfully inserted throughout pregnancy, even during latent labor, and that subsequent pregnancies occurred while the filters were still in place [48]. Neither the jugular nor the femoral routes were affected by the pregnant uterus, allowing for precise insertion of the IVC filter. No fatal PEs occurred after filter implantation in the studies that were analyzed [48]. There were no cases of fetal illness or death. When it comes to pregnant women and young women who may want to have children in the future, a suprarenal filter is the preferred option. The IVC is likely to be compressed by the expanding uterus during pregnancy.

11 Pharmacomechanical Catheter Directed Thrombolysis (PCDT)

The primary focus of apprehension regarding thrombolytic therapy during pregnancy revolves around its impact on the maternal well-being, particularly the occurrence of major bleeding. Additionally, there are concerns regarding the effects on the placenta, such as premature delivery, placental abruption, and potential fetal death. The general agreement among pertinent guidelines is that thrombolytic therapy should be reserved for cases where there is a risk of limb or life-threatening thromboembolism in pregnant individuals [49], despite the lack of large-scale studies on thrombolysis during pregnancy. In severe cases of iliofemoral DVT, PCDT is a non-invasive option. As we learn more about the treatment's efficacy and safety, it may be recommended for pregnant and postpartum women to prevent mild to severe PTS complications.

High rates of PTS have been linked to anticoagulation therapy as a monotherapy, with estimates ranging from 25% at 2 years to 46% at 5 years [50]. After 5 years, 44% of patients with iliofemoral DVT experience venous claudication, and 15% develop venous ulcers [51]. This significantly increases the risk of moderate to severe PTS.

Improvements in percutaneous catheters and stents have allowed for more individualized therapies, reducing the likelihood of widespread complications from thrombolysis. There is a lack of information regarding the use of PDCT in pregnant and postpartum patients, despite the growing prevalence of pregnancy-related DVT. PCDT may be most beneficial for these patients because they tend to be young and otherwise healthy.

Considering the hazards associated with being exposed to radiation, it is recommended that PCDT be avoided during the first trimester, when organ development occurs in the fetus. Abortion should be discussed openly if it becomes necessary [52]. When life or limb is in danger or when conservative treatment has failed, PCDT should be carried out during the second and third trimesters, using "as low as is reasonably practicable" measures to minimize radiation exposure. Given the current state of knowledge, it is not recommended for regular use in the prevention of PTS. In the event that a significant iliofemoral, DVT is found in the third trimester, the use of an IVC filter and anticoagulation should be taken into account. PDCT can also be performed as soon as delivery is deemed safe. Individuals presenting with iliofemoral deep vein thrombosis (DVT) commonly exhibit a youthful age and generally possess a state of overall well-being. Consequently, it is sensible to consider the utilization of pelvic dual computed tomography (PDCT) as a diagnostic modality during the postpartum timeframe.

12 Conclusion

Hemostasis is a crucial process that prevents blood from clotting and keeps blood vessels from bursting. Vasoconstriction, platelet plug formation, and coagulation are just a few of the complex steps involved in this process, which together prevent excessive bleeding and aid in the repair of damaged blood vessels. The coagulation cascade plays a vital role in the establishment of a stable blood clot and this involves various clotting factors. In order to prevent the mother from suffering from excessive bleeding following delivery or miscarriage, hemostasis experiences notable

alterations throughout the course of pregnancy, resulting in the development of a hypercoagulable condition. However, by these adjustments, the risk of thrombosis is also raised. This prothrombotic condition could happen as a result of combination of factors, including elevated clotting factors and venous stasis. In order to effectively treat hemostatic disorders, guarantee healthy pregnancies, and prevent thrombotic complications, a thorough understanding of the mechanisms and determinants of hemostasis is required. Additional study in this area will continue to elucidate the complex mechanisms of hemostasis, opening the door to future advances in diagnostic and therapeutic methods.

Compliance with ethical standards

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Disclosure of conflict of interest

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