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Association Between Venous Thrombosis (VT) and Pregnancy: A Literature Review

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Abstract. The incidence of VTE varies across countries, with Eastern regions generally reporting lower rates. In pregnancy, a combination of intrinsic factors, such as hormonal changes, increased blood clotting tendency, and genetic predispo-sitions, along with environmental factors like lifestyle and healthcare access, can trigger VTE through various, often overlapping mechanisms. The precise role of certain risk factors and their interactions during pregnancy remains un-clear and warrants further study. Ongoing research into pregnancy-related VTE is crucial due to the considerable number of idiopathic cases and the need to refine risk stratification methods. Understanding how different risk factors interact during pregnancy can lead to more effective prevention strategies and targeted treatments. As new risk factors are identified, they may help clarify the underlying mechanisms of VTE in pregnancy, particularly in cases where the cause is unknown. Additionally, improving risk stratification not only helps prevent the initial occurrence of VTE in pregnant women but also plays a vital role in reducing the likelihood of recurrence, ultimately leading to better out-comes for both the mother and the child, as well as more efficient use of healthcare resources.

Highlights:

1. VTE in Pregnancy: Hormonal, genetic, and environmental factors contribute.
2. Research Needs: Clarify interactions, refine risk stratification, prevent idiopathic cases.
3. Outcomes: Better maternal-child health, reduced recurrence, efficient healthcare use.

Keywords: Venous thrombosis; Thrombosis; Cerebral Venous Sinus Thrombosis; Coagulation; pregnancy.

Introduction

The term medical, venous thrombosis (VT) or as more commonly referred to as Deep Venous Thrombosis (DVT) of the leg. VT occurs around 1 in a thousand people per year [1].

Cerebral venous sinus thrombosis (CVST) in women using oral contracep-tives, or pregnancy, postpartum, or hormone replacement therapy (HRT) are risk factors for VT. Treatment of patients in this group who do not have a history of VT or who are currently

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pregnant consists in using of low molecular weight hep-arin (LMWH), which is a preferred treatment for all patients with brain bleeding [2].

In a study from China in 2016 it was found that the mean age of patients was 32.4 ±5.3 years with a median range of 29–36 years. The prevalance of VT in women was shown to be greater than that in men by finding that, of the 627 newly diagnosed cases, 4.1% were those with a history of VT, and 0.7% were recent case discov-eries. CES were performed in 14%, and thrombotic events occurred in 8.6% of these, which is the majority of births nor-mal [3].

Thrombosis is a normal physiological process that leads to obstruction of blood flowing through hollow pas-sageways or organs; and activation of thrombosis through internal and external pathways initiates a chain of body reactions to complete thrombus formation. Clot presence is risk factor of thrombus formation. Reflect-ing secondary prod-ucts from fibrin degradation is a small part of the protein, called D2D. D2D is assumed to be a sensitive indicator of the formation of thrombus [4].

Most recently, research has shown that thrombosis oc-curs most frequently in the last few decades and is asso-ciated with an increase in D2D levels, possibly inducing D2D levels above the normal threshold of 0.5 μg/mL in pregnant women [5].

Blood clots in certain areas of the body can cause thrombosis. Complications of the clotting process may also lead to thrombosis (diseases of the blood vessels), the most common caused being heart disease that results in blood vessel damage. Blood vessel integrity and pre-vention of bleeding is attributable to the occurrence of hemostasis which involves Platelets, vascular endothe-lium, plasma protein factors, natural anticoagulant pro-teins, antifibrinolytic proteins, and fibrinolytic proteins [6].

All these components must be adequately available and function properly to prevent thrombus formation and maintain hemostasis, which plays a critical role in the body's natural defense mechanisms against excessive bleeding. Anticoagulant properties includes the interac-tion between the components that prevent excessive coagulation. Hemostatic function can operate normally if there is a balance between pro-coagulant factors and anticoagulant factors.The hemostasis mechanism occurs through the contraction (narrowing) of blood vessels, adhesion, and platelet aggregation, and the involvement of active coagulation factors. This process attempts to maintain blood tissue

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and ensure that the damaged vas-cular system forms a temporary clot or plug on the walls of the damaged blood vessels [7].

This process involves three stages: platelet aggregation, formation of fibrin webs, and partial or complete disso-lution of the clot by plasmin. The process of initial platelet aggregation occurs at the site of injury, where platelets adhere to the blood vessel injury site and are activated by thrombin, which is involved in the coagula-tion cascade. This allows platelets to adhere to the col-lagen in the injury site, facilitating the coagulation pro-cess. Platelets also release Adenosine Diphosphate (ADP), which activates more platelets, and then the ad-hesion process occurs in the presence of Fibrinogen to form a Hemostatic plug or Thrombus, forming Fibrin webs or associated fibrin threads, resulting in a stronger and more stable clot [8].

Hemostasis is divided into several stages: Primary He-mostasis, Secondary Hemostasis, and Thrombus For-mation. Primary Hemostasis involves components of blood vessels and platelets, which initiate the process immediately upon bleeding by tightening the blood vessels and forming a platelet plug at the injury site. Secondary Hemostasis begins with the involvement of Coagulation Factors and Anticoagulation Factors to sta-bilize the primary hemostatic plug by forming fibrin webs. The final stage, Thrombus Formation, involves the dissolution of the fibrin web, which controls the process to prevent pathological thrombus formation [7].

Primary Hemostasis plays a role in the event of injury or damage to the endothelium, leading to the adhesion of platelets to the exposed collagen fibers. Platelets ag-gregate at the injury site, releasing contents that attract more platelets to form a platelet plug. This plug pre-vents further blood loss and initiates wound healing. However, if this process occurs in the cerebral veins, it can lead to Cerebral Venous Sinus Thrombosis (CVST). Clots can form in veins, arteries, or heart chambers, leading to various complications such as vessel occlu-sion. Thrombi are classified into Red Thrombus (Coag-ulation Thrombus), White Thrombus (Agglutination Thrombus), and Mixed Thrombus. Typically seen in venous vessel, this type of thrombus consists of RBC, fibrin, even distributed WBC and PT. An example of white thrombus is the thrombus, which consists of rela-tively small numbers of red blood cells, and a layer of platelets (PT) and white blood cells (WBC), with a fi-brin covering this layer, typi-cally seen in arteries. For example, the most common form of thrombus is the mixed thrombus

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containing both red and white thrombi; this is typically seen with deep vein thrombosis (DVT) but can also be the result of platelet activation or expo-sure to the surface [9].

But for cases of no balance between the coagulation factors and weakened walls of protection against thrombosis, blood clotting takes place. Factors included damage to the endothelial cells, the inner lining of the blood vessel (loss of endothelial cells caused by dam-aged vein lining, or cell death as a result of erosion) and activation of the platelets (PT) or the interaction of platelets with collagen beneath the endothelium. The process can be influenced by a deficiency or defect of the Von Willebrand Factor (VWF), a glycoprotein in the plasma that is central to the adhesion of platelets and collagen for primary hemostasis. The unbalance pro-motes activation of the coagulation system and the dysregulation of the fibrinolytic system, which causes thrombosis. Antithrombin III Factor, released by healthy endothelial cells is the mechanism of protection against coagulation. By Fibrinolysis, the coagulation factors are dissolved, and by Coagulation Inhibitors its active co-agulation fac-tors are identified. The starting point for this process is to inactivate active coagulation factors and platelet aggregates in the blood stream, activate the fibrinolytic system to digest fibrin clots [10].

Arterial thrombus occurs due to rapid blood flow caused by the heart's pump, which forms arterial clots from platelets primarily. On the other hand, Venous Throm-bosis (VT) forms mainly in areas of stasis and is pri-marily composed of erythrocytes, fibrin, and platelet components. One of the diseases caused by venous thrombosis is deep vein thrombosis (DVT[11].

B. Effect of Thrombosis on Blood

Thrombosis in one of the blood vessels in the human body occurs rapidly and may dissolve the clot at the site of injury. The wound healing process involves several steps that sequentially form a clot to cover the injury site. The clot acts as a temporary barrier that aids in healing. Furthermore, three factors often interact to fa-cilitate this process:

1. Blood Vessels:

When a wound occurs in a blood vessel causing bleed-ing, the blood vessel contracts, reducing the space for blood movement, allowing the clotting process to com-mence. As the blood flows out of the blood vessel, pressure and the injury to the vessel wall prevent the continuous flow of blood [12].

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2. Platelet Factors

Platelets aggregate and spread rapidly in case of any damage or cut in the blood vessel. Platelets adhere to the blood vessel walls quickly and aggregate rapidly at injury sites. Given the substantial data collected from the human body, it has been found that the platelet re-sponse to vascular injury is quick and effective, forming a stable clot that cannot easily break away.

Studies revealed that these platelets form a uniquely structured clot, distinguished by its heart-like shape, and provide robust structural stability even in states of low activation. This observation led to the conclusion that they play secondary roles in venous thrombus for-mation, with substantial evidence suggesting their sig-nificant role under low light conditions. This response is pivotal to understanding the platelets' ability to adhere and aggregate under various physiological conditions. One important protein secreted by activated platelets is Beta-Thromboglobulin (β-TG), which is released from alpha granules (a component of platelet granules) during platelet activation. This protein stimulates other plate-lets and plays a crucial role in forming blood clots within the body, containing up to 80% of growth factors. Furthermore, measuring the levels of β-Thromboglobulin in plasma provides an indication of platelet activation levels and correlates with the risk of venous thrombus formation [13].

The coagulation process aims to prevent blood loss, and recent data suggest that controlled inhibition of these platelets can provide insights into various physiological and pathological clot formation mechanisms [14].

3. Protein Factors for Blood Clotting

The damaged area in the blood vessels requires a set of protein effects that trigger the production of large amounts of protein, including prothrombin (produced by the liver) and prothrombin effects [15].

A series of biochemical processes occur, leading to the conversion of prothrombin to thrombin, which enters the clotting events at the injury site. Another factor called fibrinogen (constantly present in humans) under-goes a series of biochemical transformations to convert fibrinogen into fibrin. This forms a network of blood platelets and red blood cells that helps stop bleeding at the injury site. Thrombin transfers the essential role of clotting to the clotting system, where fibrinogen’s role is critical to maintaining the integrity of the blood ves-sels. Any disturbances in the system can lead

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to clotting disorders, resulting in primary bleeding or blood vessel blockage, and inflammation pathways play significant roles in regulating these pathways [16].

Moreover, inflammation has multiple sides to its cel-lular function. It involves various receptors and internal mechanisms. From this perspective, fibrinogen and its effects play significant roles in responding to the re-sulting material from tissue injury, leading to the heal-ing stage. This is evident in the division of the final stage into two main stages: inflammation (Willebrand factor and thrombin act significantly) and the second stage involves the dissolution of fibrinogen using plas-min, converting fibrin into soluble substances to prevent clots. Plasmin is crucial in the breakdown and enlarge-ment of blood cells, especially the activated fibrinogen, by converting it into fibrin products [17].

The usual conditions for this process are such that dis-eases like liver cirrhosis, which causes severe bleeding when significant damage or injury to blood vessels oc-curs, prevent the completion of this process. There are several proteins involved in the clotting process, in-cluding prothrombin, which is one of the clotting pro-teins produced by the liver. After a series of biochemi-cal changes, prothrombin converts to thrombin, the final product of the clotting series. Thrombin then converts to fibrinogen, resulting in the formation of fibrin, ulti-mately leading to clot formation Moreover, thrombin acts on blood platelets, influencing several factors for coagulation and inhibiting fibrinolysis. A single point mutation in the Prothrombin Gene (PTG) results in the substitution of guanine for adenine at nucleotide posi-tion 20210 on chromosome 11. This mutation, located in the 3' untranslated region of PTG, does not affect the protein structure of prothrombin. However, it leads to increased prothrombin levels in the blood, alongside increased mRNA expression. This mutation is generally associated with a hypercoagulable state [18].

The inherited prothrombin mutation G20210A during pregnancy leads to an increased state of hypercoagula-bility, which may have already been present. Normal pregnancy is associated with various changes in the co-agulation pathway, including increased levels of several coagulation factors, decreased levels of protein S, and inhibited fibrinolysis. There is also a reduction in the activity of activated protein C, an anti-inflammatory protein, these physiological changes are important for coagulation and are necessary to reduce blood loss dur-ing childbirth [19].

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Natural pregnancy is associated with various changes in the coagulation pathway. These changes include an in-crease in several clotting factors. One of these is Factor V Leiden (FVL), a mutation that increases the risk of blood clots, and a decrease in protein S levels (one of the proteins dependent on Vitamin K), and inhibits fi-brinolysis [20].

Due to its role in blood clotting, Vitamin K (K-Vitamin) is essential. To convert it to its functional form, the use of Vitamin K as a complete supplement is helpful. This vitamin has been known since ancient times to prevent bleeding and promote blood clotting. Vitamin K also plays a crucial role in physiological processes, activating many proteins involved in the clotting process over the past twenty years. These pro-teins include protein S and protein C, which depend on Vitamin K for proper function. Vitamin K is also vital in muscles, bones, adipose tissues, and bile ducts [21].

Seventeen different proteins that depend on Vitamin K have been identified so far. These proteins are found in the bone system, vascular tissues, and blood vessels. For example, osteocalcin, which deposits calcium in the bone matrix, also aids in repairing tissues and cardiac and vascular system development. This aids in protect-ing endothelial cells, prevents apoptosis of smooth muscle cells, and resists calcification of arterial walls, leading to a reduced risk of atherosclerosis. Further-more, it promotes the growth of bone cells, regulates the movement of stem cells, and impacts various body sys-tems the role of protein-induced vascular calcification, influenced by the carboxylation-dependent proteins re-lated to vitamin K, in both the cardiovascular system and bone tissue. It outlines how these proteins may have either protective or harmful effects, depending on the levels of vitamin K and its related proteins. Further-more, it discusses the potential relationship between the processes of vascular calcification and bone formation, particularly during fetal development, and suggests a link between the cardiovascular system and bone growth. [22].

C. Reasons for Venous Thrombosis:

- Prolonged immobilization or bed rest, particularly post-surgery, can significantly increase the risk of VT.
- Smoking is a major factor that increases blood viscos-ity and reduces its flow. [23].
- Certain genetic mutations, like Factor V Leiden, in-crease the risk of VT. ([24].

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- Infections such as COVID-19 or congenital deficien-cies in the coagulation cascade lead to the formation of clots inside the veins.
- Weight gain contributes to the increased risk of VT.
- Arteriosclerosis.
- Certain autoimmune diseases.
- Heart failure.
- Certain cancers can cause an abnormal rise in pro-thrombotic factors in the blood. [25].
- Pregnancy, particularly in the pelvic and lower limb regions, increases the risk of VT [26].

D. Symptoms of Venous Thrombosis:

The symptoms of venous thrombosis vary depending on the location of the blood clot, as blood continuously circulates throughout the body. If the clot travels to dif-ferent areas after forming, such as the lungs, the patient may experience symptoms like shortness of breath, chest pain, or if it moves to the leg, symptoms such as calf pain and swelling [25].

E. Types of Venous Thrombosis:

Venous thrombosis (VT) includes several types, some of which are more common and widespread, while others are less frequent [27].

E-1.The Primary Types of Venous Thrombosis:

E-1-1 Deep Venous Thrombosis (DVT):

Deep Venous Thrombosis (DVT) and venous thrombo-embolism (VT) are among the most critical health is-sues, particularly affecting women, with significant im-plications for mortality rates. Recurrent pregnancy loss, which has increasingly become a serious issue with both psychological and physical impacts, is a significant cause of deep venous thrombosis during pregnancy. It is closely related to recurrent pregnancy loss and elevated homocysteine levels. The presence of Homocysteine during pregnancy is linked to recurrent miscarriage. Elevated Homocysteine levels in the blood can lead to cardiovascular diseases and vascular diseases. In addi-tion, Homocysteine levels that are elevated in preg-nancy can cause Preeclampsia, recurrent mis-carriage and reduced fetal weight (Gusenbauer et al, 2020).28 Evaluating Homocysteine levels is essential in these patients as it is a major adverse pregnancy out-comes factor [29].

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E-1-2 Pulmonary Embolism (PE):

Blood clots or narrowings of blood vessels that become blocked by a blood clot are called Pulmonary embolism. Blood clots travel through the blood and lodge in the pulmonary arteries. It can cause blockage and is prone to severe com-plications. Symptoms range in severity from low to high risk PEs, based on type of PE. Clotting occurs in the blood vessels of the lungs and may result in serious complications. Treatment for VTE (Venous Thromboembolism) is different if the VTE is provoked or unprovoked. Long-term anticoagulant therapy is re-quired for unpro-voked VTE events; while provoked VTE events require short term anticoagulant treatment [30].

E-1-3 Cerebral Venous Thrombosis (CVT):

Cerebral venous thrombosis (CVT) is an infrequent but severe condition, the pathophysiology encom-passes thrombosis of the cerebral veins and dural sinuses, which potentially can lead to major morbidity and mor-tality. The presentation of CVT is diverse and includes headache; benign intracranial hypertension; subarach-noid hemorrhage; focal neurological dysfunction; sei-zures; unexplained change in consciousness; and me-ningoencephalitis. Cerebral vein thrombosis is a chal-lenging diagnosis because of the variable presentation, as well as the variety of risk factors. Delay in diagnosis is common, with a median delay to hospital admission of four days after symptom onset and to diagnosis of seven days after symptom onset. Therefore, there is a need to main-tain a high level of suspicion for this con-dition so as to make an early diagnosis and treatment are achieved [31].

E-2 Rare Venous Thrombosis

E-2-1 Surface Venous Thrombosis (SVT):

Surface venous thrombosis (SVT) occurs when there is a disturbance or slow movement of blood flow in the veins, leading to clot formation in the vein wall. This is an uncommon but significant type of thrombosis. It is characterized by high pressure within the veins, causing blood clots to form and potentially spread. This leads to increased pressure in the veins and triggers the coagula-tion process. The clotting mechanism is mediated by platelets and thromboxane A2 (TXA2), a chemical compound released during platelet activation [32].

There is also inflammation of the veins in the upper and lower extremities, known as phlebitis. SVT usually oc-curs when a blood clot forms in one of the superficial veins

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in the body, typically in the arms or legs. It can sometimes occur in the chest or abdomen. Superficial vein inflammation often leads to localized pain, redness, and swelling, and the affected veins become visible un-der the skin. This condition can cause complications if the clot extends to deeper veins, leading to more serious health issues [33].

E-2-2 Venous Thrombosis Migratory

Venous Thrombosis Migratory is characterized by the inflammation of a single vein, which then spreads and affects other veins in various parts of the body. Some-times, both superficial and deep veins can be involved. This type of thrombosis is known as Trousseau's syn-drome, often associated with malignancies like pancre-atic cancer or lung cancer, without displaying general symptoms [34].

E-2-3 Retinal vein occlusion (RVO)

Retinal vein occlusion (RVO) is a condition that typi-cally threatens vision. It involves the blockage of the central retinal vein or one of its branches, resulting in various symptoms or combined forms. Large epidemio-logical studies have shown that the prevalence of RVO ranges from 0.5% in middle-aged individuals to 4.6% in patients over 80 years old, with a higher incidence in older adults [35].

Factors such as high blood pressure, diabetes, smoking, obesity, increased blood viscosity, alcohol consumption, and low HDL-C levels significantly raise the risk of developing RVO. Also, it is notable thathealthy life-stylecan reduce these risks. RVO is not one disease, but rather is from numerous causes of venous occlusion and hardening of the retinal veins [36].

Clinical evidence indicates that central nervous sys-tem diseases, including brain arterial hypertension, may initiate RVO, particularly at the elderly, and that central retinal vein occlusion (CRVO) may be associated with central nervous system diseases. This type of throm-bosis raises the risk of arterial complications. There are hypotheses that the structure of the branching retinal veins may predispose to vein occlusion [37].

E-2-4 Upper Extremity Deep Vein Thrombosis (UEDVT)

Upper Extremity Deep Vein Thrombosis (UEDVT) is less common than deep vein thrombosis (DVT) of the lower extremities, accounting for only about 5% of cas-es. However, UEDVT is responsible for approximately 50% of hospital-acquired venous thromboembolisms. This type of thrombosis is highly related to the presence of central

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venous catheters, which are involved in 80% of UEDVT cases. Patients with central venous catheters face a risk of UEDVT that is nearly 2% higher than those without these catheters, Studies have shown that about 66% of patients with a peripherally inserted cen-tral catheter (PICC) experience UEDVT, which occurs due to a tube inserted into a peripheral vein that extends to the superior vena cava. UEDVT can be detected through imaging tests and can occur without symptoms. Rarely, UEDVT can occur without central venous cath-eters, affecting only about 2 in 100,000 patients. These cases are usually associated with thoracic outlet syn-drome, known as Paget-Schroetter disease, which is a type of UEDVT caused by repetitive motion and pres-sure on the veins, leading to blood clots in the arms [38].

If thrombosis is suspected due to the presence of cathe-ter, clinician should check for signs of blood flow blockage and also continues treatment for three month following removal of catheter. The introduction of pe-ripheral inserted central catheters (PICCs) has much lower rates of pulmonary embolism, at 5%. The success rate of treatment is either removal of the central cathe-ter as a single strategy [39].

Treatment for Paget-Schroetter syndrome for patients includes dissolving the thrombus and, in many cases, this is a successful way to restore the vein to normal function and a success rate of 60 percent – 80 percent. We suggest that this approach should be considered for decreasing chest outlet pressure in pati-ents with this syndrome since, not only does it resolve thrombus dis-solution and management of vein inflammation effec-tively [40].

This is a life threatening condition usually appearing because of inadequate either arterial thrombosis, mesenteric venous throm-bosis, or a combination of both. both.

E-2-5 Portal Vein Thrombosis (PVT)

Portal vein thrombosis (PVT) involves thrombosis in the hepatic vein (HV), lienalis venae (LV), and intersti-tial veins (IV). This condition is the most common type of thrombosis in the portal venous system, representing about 77% of cases among 604 patients, with 38% of these patients dealing with thrombosis in multiple veins within the portal system at the time of diagnosis. PVT is associated with significant morbidity and can lead to complications such as portal hypertension, which results in increased blood pressure within the portal venous system. This can lead to severe symptoms like liver cirrhosis and other liver-related diseases. [41].

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Given the risk of bleeding, treatment options must be carefully considered for patients with portal vein thrombosis. It's important to perform precise diagnostic evaluations to tailor treatments based on the presence and severity of symptoms, which may include anticoag-ulants [42].

E-2-6 Mesenteric Venous Thrombosis (MV):

It is a life-threatening condition caused by inadequate blood flow to the intestines, due to either arterial thrombosis, mesenteric venous thrombosis, or a combi-nation of both. This condition can lead to acute mesen-teric ischemia (AMI), where mesenteric venous throm-bosis contributes to about 5% of cases. Acute mesenter-ic ischemia is a result of the blockage of the superior mesenteric vein and often causes severe abdominal pain and bowel ischemia. Mortality rate is high — around 65 percent — in the first 30 days after surgery, and it is a dangerous condition that needs urgent medical care. This type of thrombosis (Azouz et al. 2020) needs spe-cific studies of viral infections to address this issue [43].

E-2-7 Renal Venous Thrombosis (RVT):

RVT can present with out symptoms, empha-sizing that, in the most severe form, RVT can present with hematu-ria, flank pain, nausea, vomiting, fever, anorexia, severe renal impairment, and uncontrolled hypertension. In 2020 in the same study of 218 individuals living with Primary RVT the kidney dysfunction was found to be 64% of cases as the main cause [44].

Pregnancy:

Pregnancy creates a prothrombotic environment due to hormonal and biological changes in the body. These changes include alterations in blood flow from venous stasis caused by the expanding uterus, changes in the vascular wall, and increased levels of coagulation fac-tors such as factor II, V, VII, VIII, IX, X, and von Wil-lebrand factor. Additionally, there are elevated levels of D-dimer, fibrinogen, platelet activation, and activity of natural anticoagulants like protein C, protein S, and plasminogen activator inhibitor-1. These alterations persist for up to six weeks postpartum. The risk of ve-nous thromboembolism (VTE) is highest during the postpartum period, particularly within the first six weeks after delivery. This risk is about 20 times higher in the first six weeks postpartum and 80% of thrombotic events occur within the first three weeks. The postpar-tum period also significantly increases [45].

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1.Physiological Changes During Pregnancy:

Physiological changes during pregnancy accommodate the fetus's presence and growth, involving changes in blood vessels, the heart, and other bodily functions. These changes include increases in blood volume and cardiac output. Additionally, estrogen and progesterone hormones increase, which contributes to various sys-temic changes. These physiological changes help sup-port the fetus but can also lead to an increase in plasma volume, a decrease in hemoglobin concentration, and sometimes anemia due to increased red blood cell mass. These Heart rate and other cardio-vascular functions [46].

As the fetus grows and its activity increases, the body's internal organs change. The mother physiologically be-comes as if she is about to begin bleeding and, as a re-sult, the red cell count goes up and overall blood volume increases. It also includes high levels of fibrinogen, prothrombin, and other coagulation factors to prevent hemorrhage. Even so, these changes could increase the risk of throm-bus formation. Maternal physiological changes during pregnancy serve to optimize fetal ability to deal with environmental stress. It is essential to en-sure that the fetus gets the necessary nutrition during pregnancy, also essential are the changes which are necessary to the find the balance and stability of preg-nant mother body and fetus [47].

Physiological changes that mothers experience during pregnancy are body's natural adaptation mechanism to maintain or support the growing fetus. Critical in pre-venting complications and in assuring fetal develop-ment, these changes include vascular, hematologic, re-nal, and respiratory changes. The maternal body has to adapt so that the fetus gets whatever is the required nourishment and support from the maternal circulation [48].

2. Stages of Pregnancy:

Pregnancy has different stages and with each stage dif-ferent changes and complications. Maternal health is-sues associated with gestational diabetes (GHD), hyper-tensive disorders and car-diovascular disease are related to each step, and are all necessary in reaching the birth phase. As a result, these complications can raise the risk for heart disease and vascular disorders in both the mother and fetus, resulting in premature birth or fetal loss. pErough pregnancy and postpartum, ACOG recom-mends moderate physical activity on most days of the week for at least 20 to 30 phút each day, and dur-ing pregnancy and postpartum from the release of the egg from the ovary

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through its motion through the fal-lopian tube and fertilization. Once fertilized, the ferti-lized egg then starts to divide over and over, 2 cells to 4, then 8, and so forth till it reaches the uterus and grows for 5 more days. After fertilization egg attaches to and implants in uterine wall [49].

2-1The First Stage of Pregnancy:

This stage encompasses the first three months of preg-nancy, often referred to as the embryonic phase. Within ten days of fertilization, the embryo begins forming the placenta, which attaches to the uterine wall. The hor-mone progesterone, secreted by the corpus luteum, sup-ports the early pregnancy and continues to increase until the end of the pregnancy. The placenta produces hor-mones that help maintain the uterine lining and support the embryo's development. Around the end of the first month, the embryo is about five millimeters long. This period is crucial for the mother to avoid medications unless prescribed by a doctor to prevent congenital dis-abilities. By the end of the second month, the mother's body undergoes significant changes, including rapid brain growth, formation of facial features, limbs, and internal organs. By the end of the third month, the fe-tus's head is half its body and its weight increases near-ly fivefold. Symptoms include nausea, vomiting, and an increase of size of the abdomen. Wearing a baby may also lead to greater fatigue and increased emotional sensitivity for the mother [50].

2-2The Second Stage of Pregnancy (The Middle Stage):

Fetal growth stage is the period from the fourth month up to the seventh month, when this stage starts. By the end of the fourth month of pregnancy, the amniotic fluid helps develop the fetus' organs as it begins to swallow it into the mouth. But it begins to gain weight and its or-gans become defined. By this month's end, the fetus can live outside the womb but will need intensive care. This increased appetite makes for the mother to gain weight as the fetus grows inside her. In addition the levels of hormones such as placental lacto-gen and estrogen in-crease which reduces symptoms like morning sickness [51].

2-3 The Third Stage of Pregnancy (The Last Stage):

This stage begins from start of the seventh month and continues to the end of the ninth month — during which the fetal size increases approximately 2,5 times and the birth preparation also begins. As the fetus gets heavier and more fat, it accumulates to

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bring in insulation. The respiratory and digestive system completes, getting the fetus ready for independent life outside the womb. The mature fetus' brain and nerve system keep developing and it begins to hear and see. At the ninth month, the fetus is 'ready' for birth, the head coming into the lowest position in most cases. The fetus filling the womb and unborn baby getting ready for delivery may mean the mother can have less movement [52].

Conclusion

Evaluating and preventing VTE during pregnancy and the postpartum period presents a considerable challenge, compounded by inconsistent guidelines and the absence of reliable biomarkers to aid in risk stratification. Initial studies on Global Coagulation Assays (GCAs) have demonstrated their ability to capture the hypercoagulable state unique to pregnancy—something traditional coagulation tests fail to do. Advancing towards a per-sonalized approach to VTE thromboprophylaxis using multiple biomarkers could significantly improve upon the conventional screening that relies exclusively on clinical risk factors. However, the potential use of GCAs in predicting VTE risk associated with pregnancy hinges on thorough efforts to validate their analytical and clin-ical efficacy within the obstetric population.

References

[1] G. Standby and L. R., "Effect of testing for cancer on cancer- or venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE," Cochrane Database Syst. Rev., vol. 2021, no. 10, p. CD010837, 2021.

[2] B. Durmus and L. Y., "Cerebral venous thrombosis in women of childbearing age: diagnosis, treatment, and prophylaxis during a future pregnancy," Ther. Adv. Neurol. Disord., vol. 13, p. 1756286420945169, 2020.

[3] K. Haug et al., "MetaboLights: a resource evolving in response to the needs of its scientific community," Nucleic Acids Res., vol. 48, no. D1, pp. D440–D444, 2020.

[4] W. Liu et al., "Peripherally inserted central venous catheter in upper extremities leads to an increase in D-dimer and deep vein thrombosis in lower extremities," Thrombosis J., vol. 19, no. 1, pp. 1–8, 2021.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v1i2.16

[5] M. Bellesini et al., "D-dimer to rule out venous thromboembolism during pregnancy: a systematic review and meta-analysis," J. Thromb. Haemost., vol. 19, no. 10, pp. 2454–2467, 2021.

[6] N. Kiriakopoulos et al., "Investigating stress response during vaginal delivery and elective cesarean section through assessment of levels of cortisol, interleukin 6 (IL-6), growth hormone (GH), and insulin-like growth factor 1 (IGF-1)," J. Clin. Med., vol. 8, no. 8, p. 1112, 2019.

[7] N. S. Ali et al., "Venous thromboembolism-incidence of deep venous thrombosis and pulmonary embolism in patients with head and neck cancer: a tertiary care experience in Pakistan," Int. Arch. Otorhinolaryngol., vol. 19, pp. 200–204, 2015.

[8] A. A. Penka, I. R. Massaldjieva, T. N. Chalakova, and D. B. Dimitrov, "Cerebral Venous Sinus Thrombosis—Diagnostic Strategies and Prognostic Models: A Review," 2012.

[9] N. M. A. Ibrahim, A. Z. El-Shahawy, and A. Elshabacy, "Risk of Cerebral Venous Thrombosis in Oral Contraceptive Pills Users," J. EJRNM, 2018.

[10] L. Amalia, "The Role of Platelet-Selectin as a Marker of Thrombocyte Aggregation on Cerebral Sinus Venous Thrombosis," J. Blood Med., vol. 13, pp. 267, 2022.

[11] C. Weimar, F. Masuhr, and K. Hajjar, "Diagnosis and treatment of cerebral venous thrombosis," Exp. Rev. Cardiovasc. Ther., vol. 10, no. 12, pp. 1545–1553, 2012.

[12] H. M. A. M. ElBassossy, "Psiadia punctulata major flavonoids alleviate exaggerated vasoconstriction produced by advanced glycation end products," PLoS One, 2019.

[13] H. Stevens and J. D. McFadyen, "Platelets as Central Actors in Thrombosis—Reprising an Old Role and Defining a New Character," Seminars in Thrombosis and Hemostasis, vol. 45, no. 8, pp. 802–809, 2019, Thieme Medical Publisher.

[14] C. Karatoprak, S. Uyar, G. B. Abanonu, S. Pehlevan, M. Mengüç, A. Daşkin, ... and R. Demirtunç, "Elevated Beta-Thromboglobulin and Mean Platelet Volume Levels May Show Persistent Platelet Activation in Systemic Lupus Erythematosus Patients," 2018.

[15] H. Rennert and R. A. DeSimone, "Molecular Testing for Factor V Leiden and Prothrombin Gene Mutations in Inherited Thrombophilia," in Transfusion Medicine and Hemostasis, Elsevier, 2019, pp. 903–906.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v1i2.16

[16] J. Wojta, "Commentary on 'Elevated Plasma Levels of Plasminogen Activator Inhibitor-1 Are Associated with Risk of Future Incident Venous Thromboembolism': A New Role for Plasminogen Activator Inhibitor-1—An Inhibitor of Fibrinolysis Predicts Future Venous Thromboembolic Events and Links Them to Obesity," Journal of Thrombosis and Haemostasis, vol. 20, no. 7, p. 1559, 2022.

[17] S. N. Patel and A. Shander, "Physiology and Pathology of Coagulation in Pregnancy," in Principles and Practice of Maternal Critical Care, Springer, Cham, 2020, pp. 47–57.

[18] M. Sillen and P. J. Declerck, "Thrombin Activatable Fibrinolysis Inhibitor (TAFI): An Updated Narrative Review," International Journal of Molecular Sciences, vol. 22, p. 3670, 2021, doi: 10.3390/ijms22073670.

[19] J. Padda, K. Khalid, A. Mohan, S. Pokhriyal, N. Batra, G. Hitawala, ... and G. Jean-Charles, "Factor V Leiden G1691A and Prothrombin Gene G20210A Mutations on Pregnancy Outcome," Cureus, vol. 13, no. 8, 2021.

[20] H. O. Elzein, A. A. Saad, A. A. Yousif, E. Elamin, E. K. Abdalhabib, and S. E. G. Elzaki, "Evaluation of Factor V Leiden and Prothrombin G20210A Mutations in Sudanese Women with Severe Preeclampsia," Current Research in Translational Medicine, vol. 68, no. 2, pp. 77–80, 2020.

[21] B. Tesfamariam, "Involvement of Vitamin K-Dependent Proteins in Vascular Calcification," Journal of Cardiovascular Pharmacology and Therapeutics, vol. 24, no. 4, pp. 323–333, 2019.

[22] L. Wen, J. Chen, L. Duan, and S. Li, "Vitamin K-Dependent Proteins Involved in Bone and Cardiovascular Health," Molecular Medicine Reports, vol. 18, no. 1, pp. 3–15, 2018.

[23] A. Latona, K. Hill, A. Connelly, K. Stuart, and P. Wood, "Prothrombinex®-VF in Chronic Liver Disease: Friend or Foe?," Emergency Medicine Australasia, 2022.

[24] A. Siennicka, M. Kłysz, K. Chełstowski, A. Tabaczniuk, Z. Marcinowska, P. Tarnowska, J. Kulesza, A. Torbe, and M. Jastrzębska, "Reference Values of D-Dimers and Fibrinogen in the Course of Physiological Pregnancy: The Potential Impact of Selected Risk Factors—A Pilot Study," Biomed Research International, vol. 2020, p. 3192350, 2020.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v1i2.16

[25] F. I. Mulder, N. van Es, N. Kraaijpoel, M. Di Nisio, M. Carrier, A. Duggal, and G. Raskob, "Edoxaban for Treatment of Venous Thromboembolism in Patient Groups with Different Types of Cancer: Results from the Hokusai VTE Cancer Study," Thrombosis Research, vol. 185, pp. 13–19, 2020.

[26] U. Baboolall, Y. Zha, X. Gong, D. R. Deng, F. Qiao, and H. Liu, "Variations of Plasma D-Dimer Level at Various Points of Normal Pregnancy and Its Trends in Complicated Pregnancies: A Retrospective Observational Cohort Study," Medicine, vol. 98, no. 23, pp. e15939, 2019.

[27] E. V. Kane, C. Calderwood, R. Dobbie, C. Morris, E. Roman, and I. A. Greer, "A Population-Based Study of Venous Thrombosis in Pregnancy in Scotland 1980–2005," Eur. J. Obstet. Gynecol. Reprod. Biol., vol. 169, no. 2, pp. 223–229, 2015.

[28] M. Gusenbauer and N. R. Haddaway, "Which Academic Search Systems Are Suitable for Systematic Reviews or Meta-Analyses? Evaluating Retrieval Qualities of Google Scholar, PubMed, and 26 Other Resources," Res. Synth. Methods, vol. 11, no. 2, pp. 181–217, 2020.

[29] B. Singh and P. Kaur, "COVID-19 and Acute Mesenteric Ischemia: A Review of Literature," Hematol. Transfus. Cell Ther., vol. 43, pp. 112–116, 2021.

[30] R. Sztajzel, A. Coeytaux, A. R. Dehdashti, J. Delavelle, and M. Sinnreich, "Subarachnoid Hemorrhage: A Rare Presentation of Cerebral Venous Thrombosis," Headache: J. Head Face Pain, vol. 41, no. 9, pp. 889–892, 2021.

[31] P. Tadi, B. Behgam, and S. Baruffi, Cerebral Venous Thrombosis. Treasure Island, FL, USA: StatPearls Publishing, 2024. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK459315/

[32] N. Nisio and O. Page, "Improving Functional Validation Through Analyses of Operational Problems," in 2018 SpaceOps Conf., 2018, p. 2422.

[33] N. S. Evans and E. V. Ratchford, "Catheter-Related Venous Thrombosis," Vasc. Med., vol. 23, no. 4, pp. 411–413, 2018.

[34] S. P. S. Dhami et al., "Breast Cancer Cells Mediate Endothelial Cell Activation, Promoting Von Willebrand Factor Release, Tumor Adhesion, and Transendothelial Migration," J. Thromb. Haemost., 2022.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v1i2.16

[35] P. Song, Y. Xu, M. Zha, Y. Zhang, and I. Rudan, "Global Epidemiology of Retinal Vein Occlusion: A Systematic Review and Meta-Analysis of Prevalence, Incidence, and Risk Factors," J. Global Health, vol. 9, no. 1, 2019.

[36] E. Keohane, C. N. Otto, and J. Walenga, Rodak's Hematology-E-Book: Clinical Principles and Applications. St. Louis, MO, USA: Elsevier Health Sciences, 2019.

[37] M. Gallardo et al., "Machine Learning Can Predict Anti–VEGF Treatment Demand in a Treat-and-Extend Regimen for Patients with Neovascular AMD, DME, and RVO Associated Macular Edema," Ophthalmol. Retina, vol. 5, no. 7, pp. 604–624, 2021.

[38] M. Yunce, A. Sharma, E. Braunstein, M. B. Streiff, and Y. W. Lum, "A Case Report on 2 Unique Presentations of Upper Extremity Deep Vein Thrombosis," Medicine (Baltimore), vol. 97, no. 11, 2018.

[39] C. E. A. Dronkers et al., "Diagnosing Upper Extremity Deep Vein Thrombosis with Non-Contrast-Enhanced Magnetic Resonance Direct Thrombus Imaging: A Pilot Study," Thromb. Res., vol. 163, pp. 47–50, 2018.

[40] W. Liu et al., "Peripherally Inserted Central Venous Catheter in Upper Extremities Leads to an Increase in D-Dimer and Deep Vein Thrombosis in Lower Extremities," Thromb. J., vol. 19, no. 1, p. 1, 2021.

[41] F. Turon et al., "Predicting Portal Thrombosis in Cirrhosis: A Prospective Study of Clinical, Ultrasonographic, and Hemostatic Factors," J. Hepatol., vol. 75, no. 6, pp. 1367–1376, 2021.

[42] P. G. Northup et al., "Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients with Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases," Hepatol., 2021.

[43] E. Azouz, S. Yang, L. Monnier-Cholley, and L. Arrivé, "Systemic Arterial Thrombosis and Acute Mesenteric Ischemia in a Patient with COVID-19," Intensive Care Med., vol. 46, no. 7, pp. 1464–1465, 2020.

[44] A. Mukherjee, R. Ghosh, and M. M. Furment, "Case Report: COVID-19 Associated Renal Infarction and Ascending Aortic Thrombosis," Am. J. Trop. Med. Hyg., vol. 103, no. 5, p. 1989, 2020.

[45] T. Andreea, F. Anca, and L. Liviu, "Management of Postpartum Extensive Venous Thrombosis After Second Pregnancy," Medicina (Kaunas), vol. 59, no. 5, p. 871, 2023.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v1i2.16

[46] S. K. Zachariah et al., "Management of Acute Abdomen in Pregnancy: Current Perspectives," Int. J. Women's Health, vol. 11, pp. 119–126, 2019.

[47] W. F. Rayburn, J. C. Klagholz, C. Murray-Krezan, L. E. Dowell, and A. L. Strunk, "Distribution of American Congress of Obstetricians and Gynecologists Fellows and Junior Fellows in Practice in the United States," Obstetrics & Gynecology, vol. 119, no. 5, pp. 1017–1022, 2012.

[48] S. Chauhan, B. Rishi, P. Tanwar, G. Mehdi, S. H. Arif, T. Rabbani, and A. Misra, "Therapeutic Lessons From Transfusion in Pregnancy—Effect on Hematological Parameters and Coagulation Profile," American Journal of Blood Research, vol. 11, no. 3, p. 303, 2021.

[49] M. R. Helvaci, O. Tonyali, A. Abyad, and L. Pocock, "The Safest Value of Plasma Triglycerides," World Family Medicine, vol. 17, no. 7, pp. 22–27, 2019.

[50] L. J. Yockey and A. Iwasaki, "Interferons and Proinflammatory Cytokines in Pregnancy and Fetal Development," Immunity, vol. 49, no. 3, pp. 397–412, 2018.

[51] A. Baskiran, V. Ince, E. Cicek, T. Sahin, A. Dirican, I. Balikci Cicek, and S. Yilmaz, "Efficacy of Laboratory Tests and Ultrasonography in the Diagnosis of Acute Appendicitis in Gravid Patients According to the Stages of Pregnancy," World Journal of Emergency Surgery, vol. 13, no. 1, p. 24, 2018.

[52] M. N. Shahbazi, "Mechanisms of Human Embryo Development: From Cell Fate to Tissue Shape and Back," Development, vol. 147, no. 14, p. dev190629, 2020.