

## 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 predispositions, 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 unclear 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 outcomes 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 (Gerard Stansby et al.1).2

Cerebral venous sinus thrombosis (CVST) in women using oral contraceptives, 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

pregnant consists in using of low molecular weight hep-arin (LMWH), which is a preferred treatment for all patients with brain bleeding (Durmuş et al., 2020).<sup>2</sup>

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 prevalence 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 discoveries. CES were performed in 14%, and thrombotic events occurred in 8.6% of these, which is the majority of births normal (Haug, et al., 2020).<sup>3</sup>

Thrombosis is a normal physiological process that leads to obstruction of blood flowing through hollow passageways 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. Reflecting secondary products 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 (Liu et al., 2021).<sup>4</sup>

Most recently, research has shown that thrombosis occurs most frequently in the last few decades and is associated with an increase in D2D levels, possibly inducing D2D levels above the normal threshold of 0.5 µg/mL in pregnant women (Bellesini et al., 2021).<sup>5</sup>

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 prevention of bleeding is attributable to the occurrence of hemostasis which involves Platelets, vascular endothelium, plasma protein factors, natural anticoagulant proteins, antifibrinolytic proteins, and fibrinolytic proteins (Kiriakopoulos et al., 2019).<sup>6</sup>

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 interaction 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 and ensure that the damaged vas-cular system forms a temporary clot or plug on the walls of the damaged blood vessels (Ali et al., 2015).<sup>7</sup>

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 (Penka et al., 2012).<sup>8</sup>

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 (Ali et al., 2015).<sup>7</sup>

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 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 exposure to the surface (Ibrahim et al., 2018;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 damaged 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 promotes 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 coagulation factors 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 (Amalia, 2022).<sup>10</sup>

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 Thrombosis (VT) forms mainly in areas of stasis and is primarily composed of erythrocytes, fibrin, and platelet components. One of the diseases caused by venous thrombosis is deep vein thrombosis (DVT) (Weimar et al., 2012).<sup>11</sup>

## **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 facilitate this process:

### **1. Blood Vessels:**

When a wound occurs in a blood vessel causing bleeding, 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 (ElBassossy, 2019).<sup>12</sup>

## 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 ( $\beta$ -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  $\beta$ -Thromboglobulin in plasma provides an indication of platelet activation levels and correlates with the risk of venous thrombus formation (Stevens and Fadyen, 2019).<sup>13</sup>

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 (Karato-prak et al., 2018). <sup>14</sup>

## 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 (Rennert & DeSimon, 2019).<sup>15</sup>

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 vessels. Any disturbances in the system can lead to clotting disorders, resulting in primary bleeding or blood vessel blockage, and inflammation pathways play significant roles in regulating these pathways (Wojta, 2022).<sup>16</sup>

Moreover, inflammation has multiple sides to its cellular function. It involves various receptors and internal mechanisms. From this perspective, fibrinogen and its effects play significant roles in responding to the resulting material from tissue injury, leading to the healing 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 plasmin, converting fibrin into soluble substances to prevent clots. Plasmin is crucial in the breakdown and enlargement of blood cells, especially the activated fibrinogen, by converting it into fibrin products (Patel & Shander, 2020).<sup>17</sup>

The usual conditions for this process are such that diseases like liver cirrhosis, which causes severe bleeding when significant damage or injury to blood vessels occurs, prevent the completion of this process. There are several proteins involved in the clotting process, including prothrombin, which is one of the clotting proteins produced by the liver. After a series of biochemical changes, prothrombin converts to thrombin, the final product of the clotting series. Thrombin then converts to fibrinogen, resulting in the formation of fibrin, ultimately 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 position 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 (Sillen et al., 2021).<sup>18</sup>

The inherited prothrombin mutation G20210A during pregnancy leads to an increased state of hypercoagulability, which may have already been present. Normal pregnancy is associated with various changes in the coagulation 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 during childbirth (Padda et al., 2021).<sup>19</sup>

Natural pregnancy is associated with various changes in the coagulation pathway. These changes include an increase 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 fibrinolysis (Elzein et al., 2020).<sup>20</sup>

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 proteins 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 (Tefamariam, 2019).<sup>21</sup>

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 protecting endothelial cells, prevents apoptosis of smooth muscle cells, and resists calcification of arterial walls, leading to a reduced risk of atherosclerosis. Furthermore, it promotes the growth of bone cells, regulates the movement of stem cells, and impacts various body systems. The role of protein-induced vascular calcification, influenced by the carboxylation-dependent proteins related 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. Furthermore, 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. (Wen et al., 2018).<sup>22</sup>

### **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 viscosity and reduces its flow. (Latona et al., 2022).<sup>23</sup>
- Certain genetic mutations, like Factor V Leiden, increase the risk of VT. (Siennicka et al., 2020).<sup>24</sup>
- Infections such as COVID-19 or congenital deficiencies 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. (Mulder et al., 2020).<sup>25</sup>
- Pregnancy, particularly in the pelvic and lower limb regions, increases the risk of VT. (Baboolall et al., 2019).<sup>26</sup>

## **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 different 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. (Mulder et al., 2020).<sup>25</sup>

## **E. Types of Venous Thrombosis:**

Venous thrombosis (VT) includes several types, some of which are more common and widespread, while others are less frequent (Kane et al., 2015).<sup>27</sup>

### **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 issues, particularly affecting women, with significant implications 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 addition, Homocysteine levels that are elevated in pregnancy can cause Preeclampsia, recurrent miscarriage and reduced fetal weight (Gusenbauer et al, 2020).<sup>28</sup> Evaluating Homocysteine levels is essential in these patients as it is a major adverse pregnancy outcomes factor (Singh et al, 2020).<sup>29</sup>

## **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 complications. 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 required for unprovoked VTE events; while provoked VTE events require short term anticoagulant treatment (Sztajzel et al., 2021)<sup>30</sup>.

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

Cerebral venous thrombosis (CVT) is an infrequent but severe condition, the pathophysiology encompasses thrombosis of the cerebral veins and dural sinuses, which potentially can lead to major morbidity and mortality. The presentation of CVT is diverse and includes headache; benign intracranial hypertension; subarachnoid hemorrhage; focal neurological dysfunction; seizures; unexplained change in consciousness; and meningoenitis. Cerebral vein thrombosis is a challenging 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 maintain a high level of suspicion for this condition so as to make an early diagnosis and treatment are achieved. (Tadi et al., 2024) <sup>31</sup>

## **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 coagulation process. The clotting mechanism is mediated by platelets and thromboxane A<sub>2</sub> (TXA<sub>2</sub>), a chemical compound released during platelet activation (Nisio et al., 2018). 32

There is also inflammation of the veins in the upper and lower extremities, known as phlebitis. SVT usually occurs when a blood clot forms in one of the superficial veins 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 under the skin. This condition can cause complications if the clot extends to deeper veins, leading to more serious health issues (Evans and Ratchford, 2018). 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. Sometimes, both superficial and deep veins can be involved. This type of thrombosis is known as Trousseau's syndrome, often associated with malignancies like pancreatic cancer or lung cancer, without displaying general symptoms (Dhami et al., 2022).34

## **E-2-3 Retinal vein occlusion (RVO)**

Retinal vein occlusion (RVO) is a condition that typically threatens vision. It involves the blockage of the central retinal vein or one of its branches, resulting in various symptoms or combined forms. Large epidemiological 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 (Song et al., 2019).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 that a healthy life-style can reduce these risks. RVO is not one disease, but rather is from numerous causes of venous occlusion and hardening of the retinal veins (Keohane et al., 2019).36

Clinical evidence indicates that central nervous system 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 thrombosis raises the risk of arterial complications. There are hypotheses that

the structure of the branching retinal veins may predispose to vein occlusion (Gallardo et al, 2021).<sup>37</sup>

## **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 cases. However, UEDVT is responsible for approximately 50% of hospital-acquired venous thromboembolisms. This type of thrombosis is highly related to the presence of central 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 central 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 catheters, affecting only about 2 in 100,000 patients. These cases are usually associated with thoracic outlet syndrome, known as Paget-Schroetter disease, which is a type of UEDVT caused by repetitive motion and pressure on the veins, leading to blood clots in the arms. (Yunce et al., 2018). <sup>38</sup>

If thrombosis is suspected due to the presence of catheter, clinician should check for signs of blood flow blockage and also continues treatment for three month following removal of catheter. The introduction of peripherally inserted central catheters (PICCs) has much lower rates of pulmonary embolism, at 5%. The success rate of treatment is either removal of the central catheter as a single strategy (Dronkers et al, 2018, 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 patients with this syndrome since, not only does it resolve thrombus dissolution and management of vein inflammation effectively (Liu et al., 2021), but <sup>40</sup>

This is a life threatening condition usually appearing because of inadequate either arterial thrombosis, mesenteric venous thrombosis, 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 interstitial 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. (Turon et al.2021). 41

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 anticoagulants (Northup et al., 2021).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 combination of both. This condition can lead to acute mesenteric ischemia (AMI), where mesenteric venous thrombosis contributes to about 5% of cases. Acute mesenteric 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 specific studies of viral infections to address this issue.43

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

RVT can present with out symptoms, emphasizing that, in the most severe form, RVT can present with hematuria, 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 (Mukherjee et al., 2020).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 factors such as factor II, V, VII, VIII, IX, X, and von Willebrand 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 venous 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 postpartum period also significantly increases (Andreea et al., 2023).<sup>45</sup>

## **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 systemic changes. These physiological changes help support 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 cardiovascular functions (Zachariah et al., 2019)<sup>46</sup>

As the fetus grows and its activity increases, the body's internal organs change. The mother physiologically becomes as if she is about to begin bleeding and, as a result, 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 thrombus formation. Maternal physiological changes during pregnancy serve to optimize fetal ability to deal with environmental stress. It is essential to ensure that the fetus gets the necessary nutrition during pregnancy, also essential are the changes which are necessary to find the balance and stability of pregnant mother body and fetus (Rayburn et al., 2012).<sup>47</sup>

Physiological changes that mothers experience during pregnancy are body's natural adaptation mechanism to maintain or support the growing fetus. Critical in preventing complications and in assuring fetal development, these changes include vascular, hematologic, renal, 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 (Chauhan et al., 2021).<sup>48</sup>

## 2. Stages of Pregnancy:

Pregnancy has different stages and with each stage different changes and complications. Maternal health issues associated with gestational diabetes (GHD), hypertensive disorders and cardiovascular 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. Enough pregnancy and postpartum, ACOG recommends moderate physical activity on most days of the week for at least 20 to 30 minutes each day, and during pregnancy and postpartum from the release of the egg from the ovary through its motion through the fallopian tube and fertilization. Once fertilized, the fertilized 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 (Helvaci et al., 2019).<sup>49</sup>

### 2-1The First Stage of Pregnancy:

This stage encompasses the first three months of pregnancy, 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 hormone progesterone, secreted by the corpus luteum, supports the early pregnancy and continues to increase until the end of the pregnancy. The placenta produces hormones 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 disabilities. 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 fetus's head is half its body and its weight increases nearly 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 (Yockey et al., 2018).<sup>50</sup>

### 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 (Başkıran et al., 2018).<sup>51</sup>

## **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 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 (Shahbazi et al., 2020).<sup>52</sup>

## **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.

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