

OXIDATIVE STRESS AND THROMBOPHILIA: FOCUS ON PREGNANCY-RELATED PATHOPHYSIOLOGICAL MECHANISMS

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ABSTRACT

Thrombophilia, characterized by an increased tendency to form blood clots, presents a substantial risk during pregnancy, potentially impacting maternal and fetal outcomes. This review explores the intricate relationship between thrombophilia and oxidative stress, shedding light on their combined influence on blood clot formation. Specifically, endothelial dysfunction, driven by oxidative stress, emerges as a pivotal factor in thrombophilia, setting the stage for increased platelet activation and altered coagulation factors. Factors like Factor V Leiden mutation, Prothrombin G20210A mutation, and deficiencies in antithrombin, protein C, and protein S contribute to the pro-thrombotic state observed in thrombophilia. Furthermore, inflammation, closely intertwined with oxidative stress, exacerbates the risk of blood clot formation. Inflammatory responses lead to endothelial activation, altered endothelial function, and increased adhesion molecules expression, disrupting the delicate balance between pro- and anti-coagulant factors. Chronic inflammatory conditions, such as autoimmune disorders, potentiate a persistent state of heightened clotting risk. Additionally, impaired antioxidant defenses compound the pro-thrombotic state by allowing the accumulation of reactive oxygen species, thereby contributing to oxidative stress-induced endothelial dysfunction. Understanding the interplay between these factors is crucial for tailored thrombophilia management, particularly in pregnancy. Treatment strategies encompass a multifaceted approach, including anticoagulant medications, lifestyle modifications, and targeted interventions to improve endothelial health. The complex nature of thrombophilia underscores the need for a collaborative healthcare approach, involving hematologists and high-risk pregnancy specialists. Early detection, vigilant monitoring, and timely intervention are paramount in mitigating risks for both mother and baby.

Keywords: Thrombophilia, oxidative stress, pregnancy, coagulation, thrombosis.

INTRODUCTION

Thrombophilia is a medical condition characterized by an increased tendency to form blood clots predisposing to thrombosis and increased tendency toward thrombosis. There are various genetic or acquired factors that affect the blood's clotting mechanism. Hypercoagulability represents normal physiological setting in pregnancy. However, thrombophilia in women represents the burden of pregnancy-related pathophysiological conditions and severely impact pregnancy outcomes. Women with thrombophilia are at a higher risk of developing blood clots, which can lead to conditions like deep vein thrombosis (DVT) or pulmonary embolism (PE). Thrombophilia can be hereditary (genetic) or acquired, and it's very important to identify and manage this condition before and during pregnancy to reduce the risk of complications. Intruding relations between thrombophilia and oxidative stress were found in recent literature. In the present narrative review, we try to sublime the data regarding involvement of oxidative stress biomarkers in pathophysiology of thrombophilia during pregnancy. (1, 2, 3, 4)

CURRENT PATHOPHYSIOLOGICAL CONSIDERATIONS, CLINICAL MANIFESTATIONS AND TREATMENT OF THROMBOPHILIA

Thrombophilia encompasses a spectrum of disorders characterized by an augmented proclivity of the blood to form clots (5). These intricate conditions involve disruptions in the clotting process, driven by various underlying mechanisms and factors contributing to the pathophysiology of thrombophilia. An aberration in the coagulation or fibrinolytic system induces a hypercoagulable state, significantly elevating the likelihood of experiencing a thrombotic event. This eventuality may manifest as intravascular thrombus formation in either the arterial or venous systems. Thrombophilia is closely associated with the risk of developing conditions such as deep DVT and/or venous thromboembolism (6).

The inclination to develop such a blood clot can be either inherited or acquired. Globally, the prevalence of venous thrombosis stands at less than 1 case per 1000 individuals, with an even lower incidence of approximately 1 in 100,000 among children. However, with advancing age, the frequency of these occurrences escalates significantly (7).

The current understanding of thrombophilia involves a multifaceted consideration of its pathophysiology, clinical manifestations, and treatment strategies. Thrombophilia denotes a predisposition to excessive blood clot formation, resulting from a variety of genetic or acquired factors. These factors disrupt the delicate balance of the body's coagulation system, leading to a heightened risk of thrombotic events, such as DVT or PE. There is a growing concern related to thrombophilia in pregnancy since it has been associated with an increased risk not only of pregnancy-related venous thromboembolism but also other complications, including severe preeclampsia/eclampsia, placental abruption,

hemolysis, elevated liver enzyme levels, and low platelet levels HELLP syndrome, intrauterine growth restriction, and recurrent miscarriage (8, 9).

Clinically, thrombophilia may present in various ways, ranging from asymptomatic individuals who discover their condition incidentally to those with recurrent and severe thrombotic events (10). Pregnancy-related complications and the increased risk of venous thromboembolism are significant concerns for affected individuals. Furthermore, the interplay between thrombophilia and oxidative stress has garnered attention in recent research, highlighting potential avenues for therapeutic interventions (11, 12).

Treatment strategies for thrombophilia involve a tailored approach based on individual risk factors, medical history, and the presence of any concurrent conditions. Anticoagulant therapies, both short-term and long-term, play a central role in managing thrombotic events and preventing their recurrence. Additionally, lifestyle modifications and genetic counseling may be recommended to mitigate risks associated with the condition (13, 14, 15).

ETIOLOGY OF THROMBOPHILIA: INHERITED AND ACQUIRED FACTORS

Thrombophilia may be inherited or acquired. Factor V Leiden, prothrombin gene mutation, protein C or S deficiency, and antithrombin III (AT III) deficiency are examples of well-established genetic factors linked to thrombophilia, whereas uncommon genetic defects like hyperhomocysteinemia and dysfibrinogenemia are also well-established causes of thrombophilia. Elevated activities of factors VIII, IX and XI may also be associated with this state. Although the clinical manifestation of hereditary thrombophilia varies, thrombosis can occasionally occur in rare locations such as the splanchnic veins, cerebral veins, and retinal vein. Some people never get thrombosis, some may not show symptoms until they are adults, and some develop recurrent thromboembolism before the age of 30 (5, 16). Regarding genetic mutations, there are many cases of thrombophilia linked to inherited mutations in genes such as Factor V Leiden and Prothrombin G20210A (17). These mutations can produce an overactivity of the clotting system. Factor V Leiden is the most common inherited form of thrombophilia. It involves a mutation in the gene responsible for producing Factor V, a protein that plays a role in the blood clotting process. The mutation leads to an overactive form of Factor V, making blood more prone to clotting. Prothrombin G20210A mutation is another common inherited form of thrombophilia. It involves a mutation in the prothrombin gene, leading to elevated levels of prothrombin, a clotting factor. This increases the risk of excessive blood clot formation. On the other hand, anticoagulant protein deficiencies could be responsible for thrombophilia occurrence, when there is a deficiency in natural anticoagulant proteins like protein C, protein S, or antithrombin. These anticoagulant proteins play role in the regulation of the clotting process, while their deficiency can lead to excessive clot formation. Antiphospholipid syndrome

is an autoimmune condition in which the body produces antibodies that target certain components of cell membranes. This can lead to an increased risk of blood clots due to interference with the normal clotting process. Moreover, conditions like different cancer, hormonal imbalances or autoimmune disorders can create a state of hypercoagulability, making the blood more prone to form clots. According to Virchow triad, when the inner lining of blood vessels, endothelium, becomes damaged or dysfunctional due to factors like inflammation, it can trigger abnormal clot formation. Development of blood clots could be present when normal blood flow is disrupted, in the terms of stasis or turbulence. Regarding acquired thrombophilia, some factors like prolonged immobilization, surgery, different medications (hormonal therapy), and smoking could play a main role. Trauma, surgery, pregnancy, and the use of certain drugs, such as oral contraceptives, lupus anticoagulants, and anticardiolipin antibodies, are acquired causes of thrombophilia (18, 19).

PREGNANCY-RELATED THROMBOPHILIA

As mention above, pregnancy-related thrombophilia represent the serious risk for pregnancy outcome. Pregnancy itself is a condition with increased coagulability, physiologically dedicated to prevent excessive bleeding during childbirth. Some women may have underlying thrombophilic conditions that increase their risk of developing blood clots during pregnancy. Understanding mentioned underlying mechanisms is crucial for diagnosing and managing thrombophilia (20). Treatment of thrombophilia typically involves a combination of anticoagulant medications, lifestyle modifications, and sometimes surgical interventions in severe cases. In many cases, women with thrombophilia who are pregnant or planning to become pregnant may be prescribed anticoagulant medications. These medications help prevent the formation of blood clots. The type and dosage of anticoagulant will be determined by the specific type of thrombophilia and other individual factors (21). Pregnant women with thrombophilia require careful monitoring including regular ultrasounds to assess fetal growth, as well as assessments of maternal blood clotting factors. Type of thrombophilia, any prior history of blood clots, and family history are taken into consideration when determining the best course of action. In some cases, preconception planning is important. This involves discussing the risks and developing a plan for managing thrombophilia before becoming pregnant. Managing thrombophilia in pregnancy often requires a team approach, involving obstetricians, hematologists, and other healthcare professionals with expertise in high-risk pregnancies. It's crucial for pregnant women with thrombophilia to work closely with their healthcare providers to develop a personalized care plan that addresses their specific needs and minimizes risks to both the mother and the baby. Early detection, regular monitoring, and timely intervention can greatly improve outcomes for both (22).

STATE OF HYPERCOAGULABILITY IN NORMAL PREGNANCY

Both bleeding and thromboembolic problems are more likely to occur during pregnancy. The body experiences significant hemodynamic and hemostatic changes that cause a procoagulant condition during pregnancy. Pregnant women have been found to have different concentrations of coagulation factors and fibrinolysis from non-pregnant women, and pregnancy is linked to an increased incidence of thromboembolic events. Pregnancy has been demonstrated to induce a "hypercoagulable state," which, in the absence of an increase in fibrinolytic activity, might raise the risk of thrombosis and affect delivery (23). The body changes to a hypercoagulable state in response to an increased risk of bleeding during pregnancy, particularly during delivery and the early puerperium. Plasma levels of procoagulant factors such as coagulant factors VII, VIII, X, fibrinogen, and von Willebrand factor are increased, and anticoagulant activity decreases with a resulting physiological inhibitor deficiency (reduced levels of protein S and acquired resistance to activated protein C). During pregnancy and childbirth, a natural occurrence of hypercoagulability, venous stasis, and vascular damage aligns with Virchow's classical triad for VTE (24). The heightened risk of thrombosis primarily arises from an imbalance between thromboxane B2 and prostacyclin (25), coupled with lower levels of protein S. Moreover, a hypothesis posits that the diminished activity of protein S (25) during the puerperium may contribute to this elevated risk. While various studies have delved into specific criteria, some have concentrated solely on the third trimester. This diverse focus underscores the multifaceted nature of this phenomenon.

Furthermore, the reduction in tissue plasminogen activator activity and the surge in plasminogen activator inhibitors collectively dampen the efficacy of the fibrinolytic system (27). Hemodynamic shifts, including the vasodilatory effects induced by progesterone, mechanical pressure exerted by the enlarged gravid uterus on the inferior vena cava and iliac veins, as well as delivery-related factors, all synergistically heighten the susceptibility to VTE. This complex interplay of physiological changes accentuates the intricacy of thrombotic risk during pregnancy and childbirth (28). Alterations in platelet function, the intricate cascade of blood coagulation, and the fibrinolytic process are critical physiological shifts that occur during pregnancy. These dynamic changes, alongside variations in biochemical markers indicative of platelet, coagulation, and fibrinolytic activity, collectively orchestrate a delicate balance within the hemostatic system, as mentioned above.

This intricate interplay is pivotal in ensuring the smooth progression of pregnancy. However, when these mechanisms face significant deviations from the norm, they can potentially give rise to severe complications, exerting a profound impact on pregnancy outcomes. Therefore, a comprehensive understanding of these dynamic transformations and their potential implications is imperative for effective

prenatal care and the optimization of maternal and fetal well-being.

BIOCHEMICAL MARKERS OF ALTERED HEMOSTASIS AND COAGULATION MECHANISMS IN PREGNANCY

Biochemical markers of altered hemostasis and coagulation mechanisms in pregnancy constitute a dynamic and intricate field of study. These markers encompass a range of molecular indicators that serve as windows into the complex interplay between the coagulation system and pregnancy-related physiological changes. In the following text, we made a detailed review of various Biochemical markers of altered hemostasis and coagulation mechanisms in pregnancy. D-Dimer, a product of fibrin degradation, is a widely studied marker. Elevated levels may indicate increased fibrinolysis, and are associated with conditions such as preeclampsia, gestational hypertension, and venous thromboembolism. Fibrinogen, as a key coagulation factor plays a central role in blood clot formation. Elevated levels of fibrinogen during pregnancy are considered normal, reflecting the increased demands on the coagulation system (29). Platelet count, alongside measures of platelet function, are essential indicators of the hemostatic process. Abnormalities in platelet count or function can lead to conditions like gestational thrombocytopenia or preeclampsia. Platelet counts exhibit a consistent decline throughout pregnancy across all subjects, commencing as early as the first trimester. When a woman's platelet count falls below 100,000 per cubic millimeter, it is imperative to investigate potential causes beyond pregnancy or related complications (30). Increased consumption of platelets in the utero-placental unit resulting in benign gestational thrombocytopenia with decreasing platelet counts, occasionally $< 150 \times 10^9/L$ but exceeding $80 \times 10^9/L$, particularly during the third trimester (31).

Protein S and C play a crucial role in regulating coagulation. Decreased levels can lead to a hypercoagulable state, potentially increasing the risk of thrombotic events. Activated Protein C Resistance, often assessed via the Factor V Leiden mutation, is associated with an increased risk of venous thromboembolism. Antithrombin is a natural inhibitor of blood clot formation. Reduced activity levels can lead to a hypercoagulable state. Antithrombin remains stable and protein C levels are either unchanged or slightly higher during a typical pregnancy. Protein C inhibitor levels fall, free protein S levels sharply decline, and total protein S levels decline to a lesser extent (32). It is possible to detect low protein S levels until at least 8 weeks following delivery. During a typical pregnancy, tissue factor pathway inhibitor increases significantly whereas heparin cofactor II remains largely unaltered. The activation of protein C by thrombin is caused by thrombomodulin, and soluble thrombomodulin rises throughout a typical pregnancy. Its evaluation provides valuable insights into the thrombotic risk profile. Thrombin Generation Assays measure the potential for thrombin formation, offering a comprehensive view of the coagulation process. The fibrinolytic system is activated to enhance or restore circulation in

blocked vessels, which reduces fibrin production. During a typical pregnancy, there is an increase in the inactive proenzyme plasminogen due to decreased consumption and increased synthesis. Plasma levels of tissue-type plasminogen activator rise throughout pregnancy (33). During a typical pregnancy, the urokinase-type plasminogen activator is also elevated. Elevated levels of Plasminogen Activator Inhibitor (PAI-1), an inhibitor of fibrinolysis, have been associated with conditions like preeclampsia and gestational diabetes. Monitoring the levels of coagulation Factors (II, VII, IX, X) provides critical information about the integrity of the coagulation cascade. Concentration of blood coagulation factors vary during pregnancy, with their elevation or reduction. Due to hormonal changes, especially increased estrogen levels as pregnancy progresses, blood coagulation factors XIII, XII, X, VIII, von Willebrand factor, ristocetin cofactor, FVII, and fibrinogen increase markedly during normal pregnancy (34, 35). These changes are the most pronounced at third trimester of pregnancy. Elevated levels of vWF, a key player in platelet adhesion, are associated with conditions like preeclampsia and may contribute to thrombotic risk. Fibrin formation occurs more easily during normal and complicated pregnancy than during nonpregnant conditions. Pregnancy, oral contraceptive use, and patients with activated protein C resistance have all been linked to increased or unaltered thrombin production capacities (36). The aPTT is usually normal during pregnancy but tends to decrease slightly in late pregnancy and the PT is markedly shortened; INR is usually < 0.9 during the third trimester. Bleeding times, measured by template methods, is unchanged during normal pregnancy (37).

THROMBOPHILIA IN PREGNANCY

The utero-placental unit stands as a marvel of nature, requiring intricate coordination for the survival of the developing fetus. This unique interface necessitates the establishment of a specialized circulation during pregnancy, allowing for the vital exchange of nutrients, oxygen, and carbon dioxide between the maternal and fetal circulations. This finely tuned boundary is paramount to sustaining both the maternal and fetal health. However, the establishment of this delicate utero-placental circulation is not without its challenges. The potential for bleeding and thrombotic events looms, threatening to disrupt this critical function. Thus, a myriad of physiological systems collaboratively engage to safeguard this vital process.

In the context of pregnancy, thrombophilia introduces a pivotal concern. This condition signifies an elevated propensity for abnormal blood clot formation within a pregnant woman, casting a shadow over the well-being of both the mother and the developing fetus. It's important to note that pregnancy, in and of itself, induces a state of hypercoagulability, heightening the predisposition to clotting. When coupled with thrombophilia, this risk escalates further (38). The repercussions of such a scenario are profound. Pregnant women with thrombophilia face heightened risks, potentially culminating in dire consequences. Conditions such as DVT, PE, and even stroke may arise, necessitating urgent medical

intervention (REF). Furthermore, the presence of blood clots can obstruct blood flow to the placenta, instigating potential complications for the fetus.

Thrombotic events diagnosed during pregnancy and the postnatal period can be attributed to both hereditary and acquired thrombophilia. The period surrounding birth and the postnatal phase can give rise to hemostatic issues, presenting significant complications in terms of both maternal and fetal morbidity and mortality (39). Given that pregnancy and the postnatal period are widely recognized as risk factors for thrombosis, it is established that approximately 50% of pregnant women may experience venous thromboembolism. The risk of venous thromboembolism affects approximately 1 in 1600 births (40).

This perilous situation can lead to grave outcomes, including intrauterine growth restriction, stillbirth, or preterm birth, all of which exert a profound impact on the overall outcome of the pregnancy. These challenges underscore the critical importance of meticulous feto-maternal medical care, where vigilant monitoring and timely intervention play pivotal roles in safeguarding the health and well-being of both the mother and the developing fetus.

OXIDATIVE STRESS IN WOMEN

Oxidative stress is a fundamental cellular imbalance characterized by an excess of reactive oxygen species (ROS) and a deficiency of antioxidants, leading to potential damage to cellular components. ROS, including free radicals and non-radical oxygen derivatives, are produced as natural byproducts of cellular metabolism. They play crucial roles in signaling and physiological processes. However, when ROS levels surpass the capacity of antioxidant defense systems, oxidative stress ensues, potentially leading to cellular dysfunction, tissue damage, and the initiation or exacerbation of various pathological conditions (41).

The pathophysiology of oxidative stress encompasses a complex interplay of cellular and molecular events. ROS, generated in mitochondria, peroxisomes, and through enzymatic processes, interact with biomolecules such as lipids, proteins, and nucleic acids. Lipid peroxidation, a prominent consequence of oxidative stress, leads to the formation of reactive aldehydes and other toxic metabolites, further perpetuating cellular damage (42).

Proteins, particularly enzymes and structural proteins, may undergo oxidative modification, impairing their functionality and disrupting vital cellular processes. Additionally, oxidative stress induces DNA damage, including base modifications, single- and double-strand breaks, and DNA-protein crosslinks, potentially leading to mutagenesis and genomic instability (43, 44).

Antioxidant defense mechanisms, including enzymatic (e.g., superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic (e.g., glutathione, vitamins C and E)

systems, act to counterbalance ROS production and mitigate oxidative damage. However, disruptions in these defense mechanisms, coupled with increased ROS generation, can overwhelm the cellular antioxidant capacity (45).

GENDER-RELATED OXIDATIVE STRESS PATHOLOGIES

Sex-specific disparities in oxidative stress responses and susceptibility to oxidative damage are increasingly recognized (46). Biological differences in hormonal profiles, enzymatic activities, and cellular signaling pathways contribute to gender-related variations in oxidative stress pathologies.

In females, hormonal fluctuations, particularly those associated with menstruation, pregnancy, and menopause, modulate oxidative stress responses. Estrogen, for example, exhibits antioxidant properties and influences the expression of antioxidant enzymes, providing a degree of protection against oxidative damage. Conversely, the hormonal shifts during menopause may contribute to an augmented susceptibility to oxidative stress-related conditions (47, 48).

In males, factors such as higher basal metabolic rates, increased muscle mass, and differences in hormonal profiles influence oxidative stress susceptibility. Testosterone, for instance, has been implicated in both pro- and anti-oxidant effects, with its impact on oxidative stress response pathways exhibiting context-dependent outcomes (49, 50).

Specific gender-related oxidative stress pathologies encompass conditions such as cardiovascular diseases, neurodegenerative disorders, and certain types of cancer. Understanding the intricate interplay between gender-related factors and oxidative stress responses is crucial for developing targeted therapeutic strategies and optimizing healthcare interventions tailored to both males and females.

OXIDATIVE STRESS IN DIFFERENT PREGNANCY-RELATED COMPLICATIONS

Pregnancy is a physiological state that involves significant changes in a woman's body to support the growth and development of the fetus. These changes can lead to an increase in oxidative stress, which is an imbalance between the production of ROS and the body's ability to neutralize them with antioxidants. Pregnancy and oxidative stress are related at several levels, and here we discuss on this interesting relationship in physiological and pathophysiological conditions.

During pregnancy, there is an increase in metabolic rate to meet the demands of the growing fetus. This state of increased metabolic activity can lead to higher production of ROS as a product of normal cellular metabolism (51). Moreover, hormonal changes, especially an increase in estrogen levels, can contribute to oxidative stress. Estrogen has been shown to influence ROS production and antioxidant defenses. In addition, the placenta, which is crucial for the exchange of nutrients and oxygen between the mother and

fetus, is a site of increased oxidative stress. This is due to the high metabolic activity and exposure to oxygen in this tissue. Pregnancy is associated with controlled inflammatory responses, especially during processes like implantation and labor. Inflammation is related to oxidative stress and also can lead to increased production of ROS. Pregnancy leads to an increase in blood volume and cardiac output to supply the developing fetus. This can create conditions that promote oxidative stress, especially in the circulatory system. To counteract oxidative stress, the body has natural antioxidant defense mechanisms. However, during pregnancy, the demand for antioxidants can increase, potentially leading to a state of relative deficiency (52, 53).

Excessive oxidative stress during pregnancy has been associated with various complications, including preeclampsia, gestational diabetes, preterm birth, and intrauterine growth restriction. These conditions are thought to be, at least in part, related to oxidative damage to tissues. While some level of oxidative stress is necessary for normal fetal development and signaling processes, excessive oxidative stress can be detrimental to fetal health (54). A balanced diet rich in antioxidants (such as vitamins C and E, and other phytochemicals) can help mitigate oxidative stress during pregnancy (55, 56). It's important to note that while oxidative stress can have negative effects, it also plays essential roles in normal physiological processes. Striking a balance is crucial. Pregnant individuals should consult with healthcare providers for personalized advice on managing oxidative stress during pregnancy since there is an importance of maintaining oxidative and antioxidant balance throughout pregnancy.

OXIDATIVE STRESS AND COAGULATION PROCESS

Oxidative stress is an imbalance between the production of ROS, also known as free radicals, and antioxidant defenses in the body. Research indicates that free radicals play an important role in both physiological (relating to normal body functions) and pathological (caused by or related to disease) conditions. ROS at low or moderate levels have positive effects and are involved in immune function and the defense against pathogenic microorganisms. However, in higher amounts can cause oxidative stress and potential damage. High levels also have a critical role in platelet activation and are involved in health conditions such as cancer and cardiovascular disease. Recent research has found that oxidative stress, resulting from platelets and endothelial cells are closely associated with stroke-related thrombosis (57). Oxidative stress not only promotes primary thrombus formation by destroying endothelial cells and platelets but additionally affects thrombus maturation. As the body ages, the risk of thrombosis increases, and research has shown that aging is also associated with the imbalance of oxidative stress and antioxidant status. An overproduction of ROS as we age can induce different physiological changes which are involved in all the processes associated with thrombosis development (58). As well as aging, other internal or endogenous causes of free radical production include inflammation, ischemia,

infection, cancer, excessive exercise and mental stress. Exogenous (external) risk factors include cigarette smoking, cooking (smoked meat, used oil and fat), certain drugs, heavy metals and environmental pollutants (59). Due to elevated levels of ROS in the bloodstream, a procoagulant state may be further facilitated through the oxidative modification of coagulation-associated proteins. Among the mechanisms employed by ROS, notable examples include their direct inactivation of pivotal anticoagulant proteins like protein C and its precursor thrombomodulin (60). Additionally, ROS play a prothrombotic role by oxidizing fibrinogen, expediting its conversion into fibrin (61). Additionally, they impede the binding of thrombin with anticoagulants, specifically the antithrombin III–heparin complex and thrombomodulin (62). Furthermore, ROS reduce antithrombin's ability to attach to heparin (62). Moreover, ROS directly function as chemotactic agents for neutrophils (63).

In summary, oxidative stress impairs the mechanical properties and deformability of red blood cells (RBCs), thereby influencing blood rheology and circulation. This, coupled with compromised phagocytosis of RBCs exposing phosphatidylserine (PS), hemolysis, and genetic variations, can instigate prothrombotic events in veins (64). It is known that erythrocytes showing reduced deformability and increased aggregability have prothrombotic tendency (65). Consequently, this predisposes older adults to age-related venous thrombosis or embolism specifically, and conceivably other cardiovascular conditions more broadly.

Oxidative stress is intricately implicated in all major processes underlying venous thrombosis. RBCs have been demonstrated to play a pivotal role in both hemostasis and thrombosis. They significantly influence blood coagulation not only through altering rheology and interacting with various cells, including platelets, endothelial cells, leukocytes, and coagulation factors, but also via the generation of RBC-derived microparticles (MPs) and their communication with the complement system (66). Oxidative stress within RBCs substantially amplifies their pro-coagulant potential in various manners. ROS modify the mechanical properties of RBCs, augmenting their rigidity and interactions with other cells and coagulation factors, while also stimulating the generation of MPs and exposure of PS (67). Gaining a more comprehensive understanding of the precise mechanisms through which ROS in RBCs influence the coagulation cascade could offer potential targets for developing innovative strategies to prevent or mitigate the risk and occurrence of VT/E, particularly in middle-aged to advanced-stage individuals, and potentially in other disorders characterized by excessive oxidative stress.

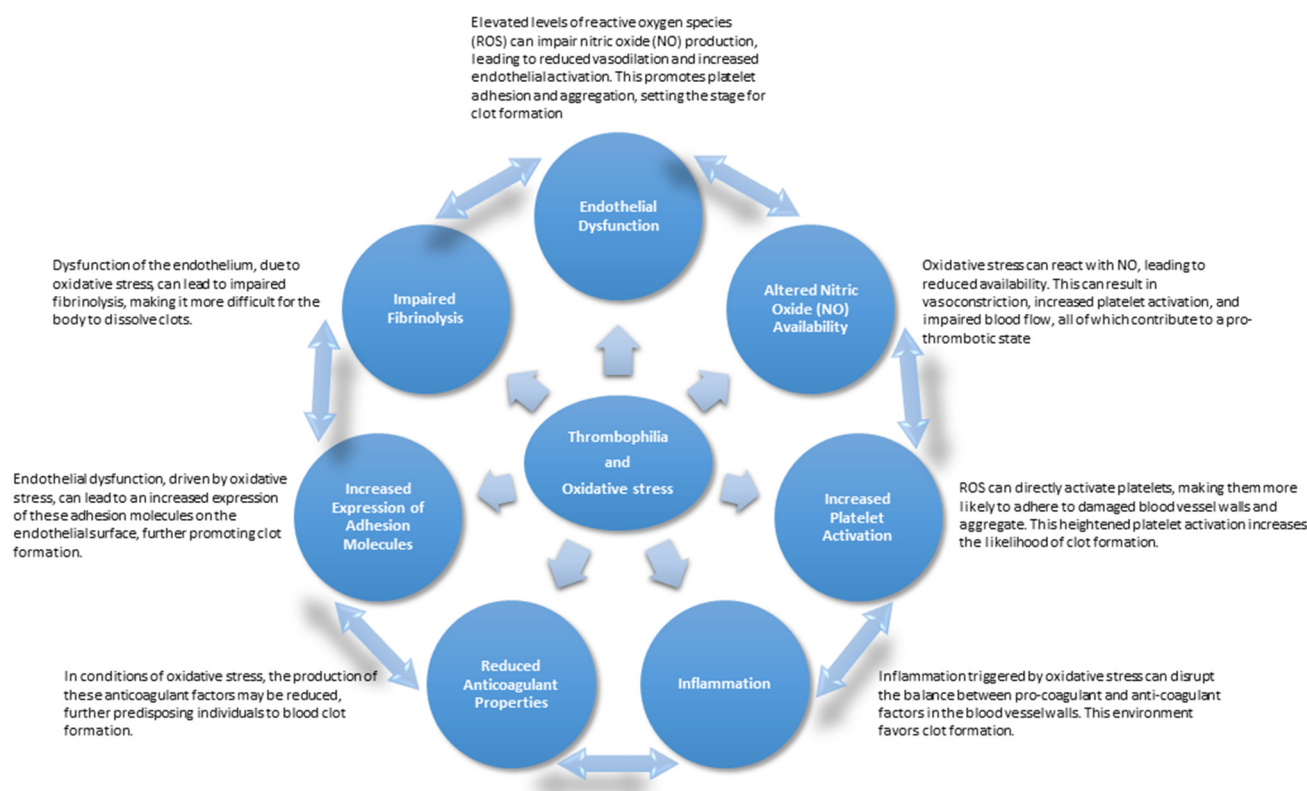
OXIDATIVE STRESS IN THE CONTEXT OF THROMBOPHILIA

Blood clot formation (thrombosis) and oxidative stress are interconnected processes in the body. While blood clotting is a crucial mechanism to prevent excessive bleeding after injury, excessive or inappropriate clot formation can lead

to serious health issues. In the context of thrombophilia, oxidative stress can contribute to the development of blood clots through several mechanisms. Numerous papers have proven that increased production of prooxidants can be present during a normal pregnancy due to the high energy demands of many body functions (53, 68, 69). The relation between oxidative stress and adverse pregnancy outcome and pregnancy complications such as preeclampsia and diabetes has been established (70). Literature data indicate that a high oxidative state of the mother corresponds to a high oxidative state of

the newborn, thus suggesting the importance of protecting the fetus before the birth process (71). Furthermore, it has been proposed that thrombophilia during pregnancy induces hemostatic response and microthrombi formation, which leads to the generation of prooxidants. Those events cause further pro-coagulation and consequently further prooxidant generation, which results in many harmful effects on the placenta and placental circulation (72, 73). The main pathophysiological mechanisms in thrombophilia regarding oxidative stress are presented in the Figure 1.

Figure 1. The main pathophysiological mechanisms between thrombophilia and oxidative stress.



ENDOTHELIAL DYSFUNCTION AND ALTERED NITRIC OXIDE (NO) AVAILABILITY

Oxidative stress can damage the endothelium leading to impaired vasodilation, increased inflammation, and altered blood flow, all of which contribute to a pro-thrombotic state (74). Particular emphasis is placed on the decrease in NO availability caused by ROS, as well as the inflammation and mitochondrial dysfunction induced by ROS; oxidative stress can lead to the breakdown of NO and reduce its availability. This impairs the endothelium's ability to maintain normal blood vessel function. Endothelial dysfunction is a condition where the endothelium, the inner lining of blood vessels, does not function properly. Endothelial cells produce NO, a molecule that helps relax and dilate blood vessels, promoting normal blood flow. In endothelial dysfunction, there is reduced NO production. This can lead to vasoconstriction

(narrowing of blood vessels) and impaired blood flow, which can contribute to blood clot formation. This can lead to various cardiovascular problems, including an increased risk of blood clot formation, which is particularly relevant in the context of thrombophilia. NO has several important roles in endothelial function. It helps prevent platelet adhesion and aggregation, inhibits smooth muscle cell proliferation, and reduces inflammation in the vessel walls. The important antioxidant enzymes crucial for neutralizing reactive oxygen species, which have the potential to deactivate NO, encompass superoxide dismutases, glutathione peroxidases, catalase, and glucose-6-phosphate dehydrogenase are decreased. Insufficiencies in these enzymes heighten oxidative stress and the deactivation of NO. Consequently, such deficiencies may contribute to endothelial dysfunction or be the foundational cause of endothelial dysfunction linked to a specific atherothrombotic risk factor (75). Endothelial dysfunction is often associated with increased inflammation and oxidative stress in the blood vessel walls. This environment can disrupt

the balance between pro-coagulant and anti-coagulant factors, favoring clot formation. There exists a significant interplay between the inflammation and coagulation systems. In this dynamic relationship, inflammation, often referred to as the "silent killer," triggers the activation of coagulation, initiating thrombosis. Conversely, thrombosis markedly amplifies inflammation. This interaction manifests in processes such as platelet activation, fibrin formation, and the functioning of natural anticoagulant pathways (76). Healthy endothelial cells produce factors that inhibit blood clotting, such as prostacyclin and tissue plasminogen activator (tPA). In endothelial dysfunction, the production of these anticoagulant factors may be reduced, further predisposing individuals to blood clot formation (77). In addition, endothelial dysfunction can lead to an increased expression of adhesion molecules on the endothelial surface. These molecules facilitate the attachment of platelets and other blood components, promoting clot formation. In addition, dysfunction of the endothelium can lead to impaired fibrinolysis, making it more difficult for the body to dissolve clots (78). Healthy endothelium has an antiplatelet effect, preventing platelets from sticking together and forming clots. In endothelial dysfunction, this balance is disrupted, leading to increased platelet activation and aggregation (79). In individuals with thrombophilia, where there is already an increased tendency to form blood clots due to genetic or acquired factors, endothelial dysfunction can exacerbate this risk. The combination of thrombophilia and endothelial dysfunction can lead to a significantly heightened risk of thrombotic events.

Managing thrombophilia in the presence of endothelial dysfunction may involve targeted interventions to improve endothelial health. This could include lifestyle modifications (such as regular exercise and a balanced diet), medications to address specific underlying causes, and close monitoring by healthcare professionals. Overall, understanding the relationship between endothelial dysfunction and thrombophilia is crucial for developing effective treatment and prevention strategies for individuals at risk of blood clot formation.

PLATELET ACTIVATION

When platelets become activated, they generate ROS as part of their response. This is a normal part of the clotting process and helps reinforce platelet activation and aggregation. Oxidative stress can stimulate platelets, the blood cells responsible for initiating clot formation. Elevated levels of ROS can stimulate platelets even in the absence of an immediate injury, potentially leading to excessive clotting. Activated platelets are more likely to adhere to damaged blood vessel walls and aggregate, leading to the formation of blood clots. Platelet activation plays a crucial role in the formation of blood clots, and in individuals with thrombophilia, this process can be heightened (80). In thrombophilia, there may be genetic or acquired factors that make platelets more responsive to activation signals. For instance, certain genetic mutations like Factor V Leiden can lead to increased activation of platelets. In addition, platelets normally adhere to the site of injury and stick together to form a plug. In

thrombophilia, platelets may aggregate more readily, leading to the formation of larger and more stable clots (81). The endothelium normally releases substances that help prevent platelets from adhering to the vessel walls. However, in thrombophilia, this balance can be disrupted, leading to increased adhesion of platelets to the endothelium. Moreover, increased secretion of platelet activating factors further enhance the clotting process. In thrombophilia, platelets may release these substances more readily, leading to enhanced clot formation (82). Imbalanced pro-coagulant and anti-coagulant factors further aggravate activation of platelets. Thrombophilia often involves disruptions in the balance between pro-coagulant (clot-promoting) and anti-coagulant (clot-inhibiting) factors. This imbalance can lead to a pro-thrombotic state, where platelet activation is favored. Moreover, platelets interact closely with coagulation factors in the blood, such as Factor VIII and Factor IX. In thrombophilia, these interactions may be altered, leading to an increased tendency for clot formation (83). Thrombophilia is particularly associated with an increased risk of DVT; platelet activation is a critical step in the formation of these venous clots. Moreover, arterial thrombosis risk is also increased: in some cases of thrombophilia, there may also be an increased risk of arterial thrombosis, where clots form in the arteries. This can lead to conditions like heart attacks or strokes (84).

Understanding how platelet activation is affected in thrombophilia is crucial for managing the condition. For individuals with thrombophilia, healthcare providers may prescribe medications that target platelet activation and aggregation, along with other interventions to reduce the risk of blood clots. Additionally, lifestyle modifications and regular monitoring are often part of the comprehensive care plan for individuals with thrombophilia.

INFLAMMATION

Oxidative stress is closely linked to inflammation. Inflammatory processes can disrupt the delicate balance between pro-coagulant and anticoagulant factors in the blood, favoring clot formation. Inflammation is closely linked to thrombophilia, and it can significantly influence the risk of blood clot formation. Inflammation can cause activation of the endothelial cells that line blood vessels. When activated, these cells can release substances that promote platelet adhesion and aggregation, contributing to the formation of blood clots (85). Inflammatory processes can impair the normal function of endothelial cells. This can lead to reduced production of vasodilators like NO, which are important for maintaining healthy blood flow. Moreover, inflammation process leads to increased expression of adhesion molecules on the surface of endothelial cells. These molecules facilitate the attachment of platelets and white blood cells, promoting clot formation (86). Disruption of pro-coagulant and anti-coagulant balance could be affected by inflammatory responses which alter the balance between pro-coagulant (clot-promoting) and anti-coagulant (clot-inhibiting) factors and towards to clot formation process. In addition activation of coagulation pathways could be affected by inflammation, activating

the coagulation system and leading to increased levels of clotting factors, which all result in promotion of pro-thrombotic state (87). Inflammatory processes can lead to the release of cytokines and other mediators that further promote blood clot formation (88). Some conditions associated with inflammation, such as autoimmune disorders (e.g., systemic lupus erythematosus), vasculitis, and inflammatory bowel disease, are also associated with an increased risk of thrombophilia (88). Chronic inflammation, as seen in certain chronic diseases, can lead to a persistent state of heightened clotting risk. This can contribute to the development of thrombophilia. It's important to note that the relationship between inflammation and thrombophilia is complex and can vary depending on the specific underlying cause of thrombophilia, as well as individual factors.

REDUCED ANTICOAGULANT PROPERTIES

Reduced anticoagulant properties, particularly in the context of oxidative stress, can significantly contribute to an increased risk of blood clot formation. Anticoagulants are substances in the body that inhibit the formation of blood clots. They counterbalance the action of pro-coagulant factors, ensuring that blood flow remains smooth and uninterrupted. Healthy endothelial cells lining blood vessels play a crucial role in regulating coagulation. They produce anticoagulant substances that help prevent excessive clotting, such as prostacyclin and tPA. Oxidative stress involves an imbalance between the production of ROS and the body's ability to neutralize them; increased ROS can cause damage of endothelial cells which leads to endothelial dysfunction. One consequence of impaired endothelial function is a reduction in the production of anticoagulant factors (89, 90). Prostacyclin is an important anticoagulant produced by endothelial cells, which inhibits platelet aggregation and promotes vasodilation. Oxidative stress can lead to reduced availability of nitric oxide, which is needed for the production of prostacyclin. This can diminish the anticoagulant properties of the endothelium. tPA is an enzyme produced by endothelial cells that plays a crucial role in the breakdown of blood clots (fibrinolysis). It converts plasminogen into plasmin, which can dissolve the fibrin mesh of a clot. In conditions of oxidative stress-induced endothelial dysfunction, there may be a reduction in the production of tPA. This can hinder the fibrinolytic process, making it more difficult to dissolve clots. ROS can directly interact with and inhibit the activity of certain anticoagulant factors. This interference can further tip the balance towards a pro-coagulant state. When anticoagulant properties are compromised due to oxidative stress-induced endothelial dysfunction, the risk of blood clot formation is heightened. Clots may form more readily and persist longer, increasing the risk of thrombotic events.

In summary, oxidative stress-induced endothelial dysfunction can lead to reduced anticoagulant properties in several ways. This includes diminished production of anticoagulant factors like prostacyclin and tPA, as well as impaired availability of NO. These alterations create an environment

that favors blood clot formation, contributing to a pro-thrombotic state.

INCREASED EXPRESSION OF ADHESION MOLECULES

Adhesion molecules are proteins on the surface of endothelial cells that facilitate the attachment of platelets and other blood components. Oxidative stress damages endothelial cells, leading to their dysfunction. In response to such a damage, the endothelium upregulates the expression of adhesion molecules. This increased expression promotes the adhesion of platelets and white blood cells, initiating the formation of blood clots. As noted above, inflammation is closely associated with oxidative stress and plays a significant role in thrombosis. Inflammatory mediators, induced by oxidative stress, stimulate the endothelium to increase adhesion molecule expression. This creates a pro-inflammatory and pro-thrombotic environment, further promoting blood clot formation (91). ROS can activate specific signaling pathways within endothelial cells that lead to increased adhesion molecule expression. This signaling cascade is a direct consequence of oxidative stress and contributes to endothelial dysfunction. Oxidative stress, by reacting with NO, reduces its availability, while its reduction contributes to endothelial dysfunction and enhances the expression of adhesion molecules, further promoting clot formation. There's a reinforcing loop between oxidative stress, inflammation, endothelial dysfunction, and adhesion molecule expression. Oxidative stress induces inflammation, which exacerbates endothelial dysfunction. This dysfunctional endothelium, in turn, amplifies adhesion molecule expression, creating a feedback loop that sustains a pro-thrombotic state. Understanding the intricate relationship between increased adhesion molecule expression and oxidative stress provides insights into the mechanisms underlying thrombophilia.

IMPAIRED FIBRINOLYSIS

After a blood vessel is injured, a cascade of events occurs to form a blood clot. This involves the conversion of fibrinogen (a soluble protein) into insoluble fibrin fibers. Fibrin forms a mesh-like structure that traps blood cells to create a stable clot. Fibrinolysis is the process by which the body dissolves these clots once the injury is healed. This process prevents the formation of unnecessary or excessive clots. Plasmin is a naturally occurring enzyme that plays a central role in fibrinolysis. It works by cleaving the fibrin mesh, breaking it down into smaller fragments that are easily cleared from the circulation.

Oxidative stress, characterized by an excess of ROS can damage the endothelial cells lining the blood vessels. tPA is an enzyme produced by endothelial cells. It plays a crucial role in fibrinolysis by converting plasminogen into active plasmin. However, when the endothelium is dysfunctional due to oxidative stress, it may produce less tPA. PAI-1 is a molecule produced by endothelial cells. PAI-1 inhibits the activity of tPA. In conditions of endothelial dysfunction,

there may be an increased production of PAI-1, further limiting the conversion of plasminogen to plasmin. The normal balance between tPA and PAI-1 is crucial for efficient fibrinolysis. Oxidative stress can disrupt this balance, tilting it towards reduced tPA activity and increased inhibition by PAI-1. With reduced tPA activity and increased PAI-1 levels, the conversion of plasminogen to plasmin is hindered. This means that there is less plasmin available to break down the fibrin mesh in the blood clot. Due to impaired fibrinolysis, the clots may persist longer than necessary, increasing the risk of complications associated with blood clots, such as DVT or PE. Oxidative stress-induced endothelial dysfunction disrupts the normal fibrinolytic process by reducing the production and activity of tPA, while increasing the levels of PAI-1. This altered balance impairs the generation of plasmin, making it more difficult for the body to dissolve blood clots, potentially leading to thrombotic events (92). Understanding these mechanisms is crucial for developing interventions to mitigate the risks associated with thrombophilia. In some cases of thrombophilia, there may be alterations in the production or activity of key components involved in fibrinolysis, such as tissue tPA and PAI-1. Reduced tPA Activity: Some forms of thrombophilia can be associated with reduced activity of tPA, which is responsible for converting plasminogen to plasmin, the enzyme that breaks down fibrin clots. This reduction in tPA activity can impair the body's ability to dissolve blood clots effectively. Thrombophilia can sometimes lead to elevated levels of PAI-1, a molecule that inhibits the activity of tPA. High levels of PAI-1 can further hinder the conversion of plasminogen to plasmin, contributing to impaired fibrinolysis. Thrombophilia can disrupt the normal balance between tPA and PAI-1, shifting it towards reduced tPA activity and increased inhibition by PAI-1. This alteration can hinder the generation of plasmin and make it more challenging for the body to dissolve blood clots.

IMPAIRED ANTIOXIDANT DEFENSE

In conditions of oxidative stress, the body's antioxidant defenses may be overwhelmed. This can further exacerbate the damage caused by ROS and contribute to the pro-thrombotic state. Impaired antioxidant defense in thrombophilia refers to a condition where the body's ability to neutralize harmful molecules as ROS is compromised. This can contribute to oxidative stress, a state where there is an imbalance between the production of ROS and the body's capacity to remove them. In the context of thrombophilia, impaired antioxidant defense can exacerbate the risk of blood clot formation through several mechanisms. Impaired antioxidant defense allows ROS to accumulate in the body. These molecules can damage cells, including endothelial cells lining blood vessels. This damage can contribute to endothelial dysfunction, a condition that promotes blood clot formation. ROS can react with NO, a potent vasodilatory agent which is shown to inhibit platelet adhesion, aggregation, and stimulate disaggregation of preformed platelet aggregates. In conditions of increased oxidative stress, NO availability can be reduced, leading to impaired blood vessel function and a pro-thrombotic state (93). ROS can directly activate platelets,

making them more likely to adhere to damaged blood vessels and aggregate, which are key steps in the formation of blood clots. As noted above, oxidative stress can trigger inflammation, which is closely linked to thrombosis. Inflammatory processes can disrupt the balance between pro-coagulant and anti-coagulant factors in the blood; ROS can influence the activity of various coagulation factors, impair fibrinolysis, and alter endothelial function, potentially promoting a pro-clotting environment. Addressing impaired antioxidant defense in thrombophilia may involve strategies to enhance the body's ability to neutralize ROS (94, 95, 96). Antioxidants, which neutralize ROS, can potentially modulate platelet activation. Studies have suggested that antioxidants may have a protective effect against excessive platelet activation (97). This can include lifestyle modifications (such as a diet rich in antioxidants), regular exercise, and in some cases, antioxidant supplements. Additionally, managing any underlying conditions contributing to impaired antioxidant defense is important. Oxidative stress can influence the activity of various coagulation factors, potentially promoting a pro-clotting environment. While oxidative stress is a contributing factor in thrombophilia, it's important to note that thrombophilia is a complex condition with multiple underlying causes, including genetic mutations and acquired factors. The interplay between oxidative stress and these other factors can vary regarding inter-individual variations. It's important to note that the relationship between oxidative stress, impaired antioxidant defense, and thrombophilia is complex and can vary depending on the specific type of thrombophilia and individual factors, while use of different antioxidative agents is challenging during pregnancy (54).

In the context of thrombophilia, a condition characterized by an increased tendency for abnormal blood clot formation, antioxidants may hold therapeutic potential. They may help mitigate the heightened risk of thrombosis associated with thrombophilic conditions. However, it's important to note that while antioxidants offer promise in modulating thrombotic risk, their clinical application requires careful consideration. Dosage, specific antioxidants, and individual patient characteristics all factor into their potential efficacy. Managing thrombophilia often involves addressing both the underlying causes and associated risk factors, which may include strategies to mitigate oxidative stress. This can include lifestyle modifications (such as a balanced diet rich in antioxidants), regular exercise, and in some cases, antioxidant supplements. However, any specific treatment plan should be developed in consultation with a healthcare provider.

Conditions associated with high levels of oxidative stress, such as diabetes, hypertension, and smoking, are also risk factors for thrombosis. Understanding the relationship between blood clot formation and oxidative stress is crucial in the context of various medical conditions, including cardiovascular diseases, DVT, and PE. Managing oxidative stress through lifestyle modifications (such as a balanced diet, regular exercise, and avoiding smoking) and, in some cases, medical interventions, can be an important component of preventing excessive blood clot formation.

In conclusion, the interplay between antioxidant activity and thrombosis underscores the significance of oxidative stress in coagulation dynamics. Understanding the intricate mechanisms by which antioxidants influence thrombotic processes provides a promising avenue for the development of targeted therapeutic strategies aimed at preventing or mitigating thrombotic events. Further research in this field holds the potential to advance our knowledge of thrombosis prevention and treatment.

SPECIFIC ANTIOXIDANT ENZYMES AND THEIR RELATION TO MECHANISMS OF THROMBOSIS

Catalase

Catalase is an enzyme found in cells, particularly in the peroxisomes of eukaryotic cells. It plays a crucial role in protecting cells from damage caused by ROS, which are highly reactive molecules containing oxygen. Catalase is one of the body's primary defenses against oxidative stress. Catalase helps convert harmful hydrogen peroxide (H_2O_2) into water and oxygen, reducing oxidative stress. This process helps prevent the accumulation of hydrogen peroxide, which can lead to cell damage and contribute to oxidative stress (98). However, catalase could interact in several crucial mechanisms related to thrombosis. The endothelial cells lining blood vessels are particularly vulnerable to oxidative damage. Catalase, by reducing the levels of hydrogen peroxide, helps protect these cells from oxidative stress, thereby supporting healthy endothelial function. While catalase primarily works in cells, it indirectly affects platelet function. Platelets can generate ROS as part of their activation process. By reducing oxidative stress in the surrounding environment, catalase may help modulate platelet activity. Catalase is part of the body's larger antioxidant defense network, which includes other enzymes like superoxide dismutase and glutathione peroxidase. Together, these enzymes work to neutralize ROS and mitigate oxidative stress. By reducing oxidative stress and protecting endothelial cells, catalase may contribute to a more favorable environment for blood flow and reduce the risk of abnormal clot formation. While catalase plays a crucial role in cellular defense against oxidative stress, it's important to note that the relationship between catalase and thrombophilia is complex and can be influenced by various factors. Moreover, thrombophilia is a multifaceted condition, and addressing oxidative stress is just one aspect of its management.

Superoxide dismutase

Superoxide dismutase (SOD) is an important antioxidant enzyme that plays a crucial role in protecting cells from damage caused by ROS. In the context of thrombophilia, which involves an increased tendency to form blood clots, the role of SOD relates to its ability to mitigate oxidative stress. Superoxide dismutase is a critical antioxidant enzyme that helps protect cells from damage caused by superoxide radicals, a type of ROS. It accomplishes this by converting superoxide

radicals into less harmful molecules, like hydrogen peroxide and oxygen. Endothelial cells lining blood vessels are particularly susceptible to oxidative damage. SOD helps protect these cells by reducing superoxide radicals, which can contribute to endothelial dysfunction. In addition, by reducing superoxide radicals, SOD may help modulate platelet activity. SOD's ability to reduce oxidative stress has a positive impact on vascular function. By preserving the function of blood vessels, SOD may contribute to a healthier vascular system and reduce the risk of abnormal clot formation. As a catalase, SOD is part of the body's larger antioxidant defense network, which includes other enzymes like glutathione peroxidase. Together, these enzymes work in concert to neutralize ROS and mitigate oxidative stress. By reducing oxidative stress and protecting endothelial cells, SOD may help create an environment that is less conducive to excessive clot formation. Some studies have explored the potential therapeutic benefits of exogenous SOD or strategies to enhance endogenous SOD activity in conditions associated with oxidative stress, including cardiovascular disorders like thrombophilia (99). It's important to note that while SOD is a critical component of the body's defense against oxidative stress, it is just one aspect of the complex interplay between antioxidants, ROS, and thrombophilia.

Glutathione

Glutathione (GSH) is a crucial antioxidant molecule found in cells throughout the body. It plays a key role in protecting cells from damage caused by ROS and other harmful molecules. In the context of thrombophilia, which involves an increased tendency to form blood clots, the role of GSH is related to its ability to mitigate oxidative stress. Glutathione is a powerful antioxidant that exists in both reduced (GSH) and oxidized (GSSG) forms. Its primary function is to protect cells from damage by neutralizing ROS and other harmful molecules (100). The endothelial cells lining blood vessels are particularly vulnerable to oxidative damage. Glutathione helps protect these cells from oxidative stress, influencing the homeostatic milieu in endothelium. Glutathione is a central player in the body's antioxidant defense network. It works in concert with other antioxidants like superoxide dismutase, catalase, and various vitamins (such as vitamin C and vitamin E) to neutralize ROS and mitigate oxidative stress. Glutathione plays a crucial role in the detoxification of harmful compounds, including environmental toxins, heavy metals, and drugs. This detoxification process helps prevent damage to cells and tissues. Some studies suggest that glutathione may have a modulatory effect on platelet activity. By reducing oxidative stress, glutathione may help regulate platelet function and prevent excessive clot formation. By reducing oxidative stress and protecting endothelial cells, glutathione may reduce the risk of abnormal clot formation. Strategies to enhance glutathione levels, either through dietary interventions or supplementation, have been explored in various medical conditions associated with oxidative stress, including thrombosis (101).

CONCLUSION

In conclusion, the intricate interplay between thrombophilia, oxidative stress, and altered coagulation factors unveils a multifaceted landscape of risk for blood clot formation. Endothelial dysfunction, exacerbated by oxidative stress, emerges as a critical player in the pathophysiology of thrombophilia. This dysfunction sets the stage for increased platelet activation, altered anticoagulant properties, and disrupted endothelial-platelet interactions, culminating in an augmented pro-thrombotic state. Furthermore, inflammation, a closely associated partner of oxidative stress, further amplifies the risk of thrombosis by disrupting the balance between pro- and anti-coagulant factors. Chronic inflammatory conditions add a layer of complexity, sustaining a heightened propensity for clot formation. Impaired antioxidant defenses exacerbate oxidative stress, perpetuating the pro-thrombotic environment. The comprehensive understanding of these intricate relationships forms the cornerstone of effective thrombophilia management. Tailored treatment plans, involving anticoagulant medications, lifestyle modifications, and targeted interventions to enhance endothelial health, are imperative. A collaborative healthcare approach, encompassing obstetricians, hematologists, and high-risk pregnancy specialists, is essential for optimizing outcomes for both mother and baby. Early detection, vigilant monitoring, and timely intervention are pivotal in mitigating risks associated with thrombophilia. Personalized care plans, taking into account individual risk factors, type of thrombophilia, and medical history, are paramount. This holistic approach empowers individuals at risk of blood clot formation to navigate their journey towards safer pregnancies and improved overall health. In essence, this comprehensive understanding not only unravels the complex web of thrombophilia but also paves the way for targeted interventions that hold the promise of significantly improving outcomes and enhancing the quality of life for individuals facing this challenging medical condition.

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