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# THE ROLE OF THROMBOPHILIA IN RECURRENT PREGNANCY LOSS

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## ABSTRACT

Recurrent Pregnancy loss (RPL) represents a major health problem, with approximately 15-20 % of all clinically recognized pregnancies resulting in pregnancy unhappy end. Recurrent pregnancy loss (RPL) defined as 3 consecutive pregnancy losses before 20 weeks it affects approximately 1% to 2% of women. Recurrent pregnancy loss exacts a devastating emotional toll on patients' lives. Each miscarriage brings with it a profound sense of loss and frustration. The association between thrombophilia and recurrent pregnancy loss (RPL) has become an undisputed fact. Development of thrombosis in pregnancy is multifactorial due to the physiologic changes of pregnancy which induce a relative hypercoagulable state as well as physical changes leading to increased stasis and also the effects of both the inherited and the acquired thrombophilias. In this review, we discuss the role of each of these factors on the development of thrombophilia as well as the evidence for the impact of pregnancy associated thrombosis on pregnancy outcome.

**KEY WORDS:** Thrombophilia, Spontaneous abortion, Recurrent pregnancy loss.

## INTRODUCTION

Thrombophilia can be defined as a predisposition to form clots inappropriately. Thrombotic events are increasingly recognized as a significant source of mortality and morbidity the

predisposition to form clots can arise from genetic factors, acquired changes in the clotting mechanism, or, more commonly, an interaction between genetic and acquired factors.[1]A successful pregnancy requires a well developed placenta and sufficient placental function to sustain an adequate fetomaternal microcirculation and the normal coagulation pathway is pivotal for the pregnancy outcomes. Also any kind of disorder in coagulation pathway may cause thrombophilia that may be the reason of placental insufficiency and PL. Recently; it has become clear that prothrombotic changes are associated with a substantial proportion of these fetal losses. Therefore, the role of thrombophilias in RPL has generated a great deal of interest. This heterogeneous group of disorders results in increased venous and arterial thrombosis. Although some thrombophilic states in RPL may be acquired such as antiphospholipid antibody syndrome (APAS).[2] Pregnancy may be compromised by prothrombotic disorders leading to subsequent miscarriages. The term thrombophilia refers to inherited or acquired conditions that predispose individuals to thromboembolic events.

Thrombophilias have been implicated in a variety of obstetrical complications including preeclampsia (PE), intrauterine growth restriction (IUGR), placental abruption, and fetal loss.[3]

**Inherited thrombophilia**

Inherited thrombophilia are the leading cause of maternal Thromboembolism and are associated with an increased risk of certain adverse recurrent miscarriage including second- and third-trimester fetal loss, abruptions, and severe intrauterine growth restriction, and early onset, severe preeclampsia.[4] Inherited thrombophilia are the leading cause of maternal thrombo embolism and are associated with an increased risk of certain adverse recurrent miscarriage including second and third trimester fetal loss, abruptions, severe intrauterine growth restriction, and early-onset, severe preeclampsia.[5] Current information suggests that all patients with a history of prior venous thrombotic events and those with these characteristic adverse pregnancy events should be evaluated for thrombophilia Current information suggests that all patients with a history of prior venous thrombotic events and those with these characteristic adverse pregnancy events should be evaluated for thrombophilia. The most common inherited thrombophilic disorders are deficiencies of antithrombin III, protein C and protein S, Factor V Leiden mutation, methylene tetrahydrofolate reductase (MTHFR) and prothrombin gene mutation (G20210A).[4]

**Prothrombin gene mutation (G20210 mutation)**

Prothrombin is a protein in the blood that is required for the blood to clot. It is also called factor II. It is a vitamin K-dependent protein which is synthesized in the liver and circulates with a half-life of approximately three to five days. Vitamin K acts as a cofactor for posttranslational gamma-carboxylation of prothrombin which is required for functional activity. Blood clots are composed of a combination of blood platelets and a meshwork of the blood clotting protein fibrin. Prothrombin is a blood clotting protein that is needed to form fibrin. If somebody has too little prothrombin, he or she has a bleeding tendency.[6]

Prothrombin gene (G20210A) mutation is associated with an increased risk of thrombosis and it is the most identifiable risk factor for venous thrombosis and is in fact the second most common genetic defect for inherited thrombosis, with Factor V Leiden being the most common. It is an autosomal dominant disorder, with Heterozygotes being at a 3- to 11-fold greater risk for thrombosis in both men and women and for all age groups. Although homozygosity is rare, inheritance of two 20210A alleles would increase the risk for developing thrombosis.[1]

The mutation leads to an increased amount of thrombin circulating in the person's blood stream. The exact mechanism by which the prothrombin gene mutation results in a thrombophilic state is unclear. It is thought that the increased amount of circulating prothrombin provides a springboard upon which the clotting cascade can get started and that, in some circumstances, it may run out of control because of that springboard potential. The prothrombin gene mutation (PT) is signaled by a defect in clotting factor II at position G20210A and the human prothrombin gene spans 21 kb on chromosome 11p11-q12 and consists of 14 exons and 13 introns, which account for 90 percent of the sequence. This mutation occurs as a result of the G to A transition at nucleotide 20210 in the prothrombin gene. The reported prevalence in Europe is around 2%to 6% and the risk of venous thrombosis to heterozygous carriers is three times the normal population.[7] More recent studies have shown that G20210A mutation is associated with RM and other studies found that the incidence of G20210A mutation was rare in women with RM.[8, 9]

**Factor V Leiden mutation**

Factor V is one of the essential clotting factors in the coagulation cascade. Its active form, factor Va, acts as a cofactor allowing factor X to stimulate the conversion of prothrombin to thrombin. Thrombin is then able to cleave fibrinogen to fibrin and a fibrin clot is formed.

Activated protein C is a natural anticoagulant it limits the extent of clotting by destroying factor V and reducing further thrombin formation. Factor V Leiden (FVL) mutation (named after the Dutch university where it was discovered) is a point mutation in the gene for clotting factor V. It has autosomal dominant inheritance and is the most common cause of inherited thrombophilia the mutation of Factor V Leiden causes acquired protein C resistance, resulting in thrombophilia both in veins and spiral arteries of the placenta.[10] The association between the FVL mutation and RPL seems stronger for non-recurrent second-trimester pregnancy loss compared with recurrent early pregnancy loss.[11] Women with factor V Leiden have a substantially increased risk of clotting in pregnancy (and on estrogen-containing birth control pills or hormone replacement) in the form of deep vein thrombosis and pulmonary embolism. They also may have a small increased risk of preeclampsia, may have a small increased risk of low birth weight babies, may have a small increased risk of miscarriage and stillbirth due to either clotting in the placenta, umbilical cord, or the fetus (fetal clotting may depend on whether the baby has inherited the gene) or influences the clotting system may have on placental development.[12]

**Methylene tetrahydrofolate reductase deficiencies**

Methylene tetrahydrofolate reductase (MTHFR) is one of the main regulatory enzymes in the metabolism of homocysteine that catalyses the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.[13]

Methylene tetrahydrofolate reductase (MTHFR) is a rare genetic defect that leads to complications in pregnancy.[14] MTHFR gene produces an enzyme called methylene tetrahydrofolate reductase and mutation in the gene inhibits the production of this enzyme, result in hyperhomocystinemia, which is an elevated level of an enzyme homocysteine found in blood plasma. When the body is deficient in methylene trahydrofolate reductase, its ability to absorb folate, such as folic acid, is inhibited. Folic acid and B9 are both essential to the development and health of the fetus. Because of a mother with MTHFR ’inability to efficiently metabolize folic acid and vitamin B9, the disorder has been linked to a variety of pregnancy complications such as congenital malformations. Elevated levels of homocysteine have been associated with placental disease, preeclampsia and RPL.[15]

Mutations in MTHFR gene lead to decreased activity of enzyme and hyperhomocystinemia, which induces platelet aggregation through promotion of endothelial oxidative damage. Although several mutations within the MTHFR gene but C677T and A1298C mutations are

the two most common mutations.[16] Single-nucleotide polymorphisms (SNPs) in metabolic pathways, which regulate enzymes such as MTHFR, are considered to be risk factors for thrombophilia. MTHFR is the key enzyme in folate, methionine, and homocysteine metabolism. The disturbances in MTHFR activity could be the cause of increased serum level of homocysteine. Hyperhomocystinemia is a risk factor for changes in coagulation cascade through direct Cytotoxic influence on endothelium, atherogenesis, activation of coagulation factor V and VII, increased level of thrombin, platelet aggregation, and a tendency toward venous thrombosis.[17]

**Factor XII**

Factor XII (Hageman factor) is an important protease that plays a major role in the initiation of the intrinsic pathway of blood coagulation and fibrinolysis and kinin formation. Although congenital factor XII deficiency (up to 50% of normal) is not associated with a clinical bleeding tendency, it can be identified on a routine coagulation test, such as a prolonged activated partial thromboplastin time.[18] This deficiency is a rare autosomal recessive disorder. It is still unclear whether factor XII deficiency causes any disorders during pregnancy. Disruption of this system may be a risk factor for early pregnancy losses and recurrent miscarriages and placental abruption were reported in cases with factor XII deficiency.[19] It is well known that congenital thrombophilia is associated with fetal loss and to cause significant maternal complications, and possibly has an adverse effect on normal fetal development (Inomo, *et. al*., 2008). Thus, factor XII deficiency and hypo fibrinolysis (mainly high plasminogen activator inhibitor activity) are the most frequent hemostasis-related abnormalities found in unexplained primary recurrent aborters. In patients with antiphospholipid antibodies or hypo fibrinolysis, there is a non-inflammatory ongoing chronic elevation of markers of endothelial stimulation associated with coagulation activation.[20]

**Protein C and Protein S deficiencies**

Protein C inactivates factor Va and VIIIa involved in the anticoagulant process and this function is enhanced in the presence of protein S. Protein C deficiency results from a decrease in protein C antigen or the activity of protein C also Protein C is a 62-kD, vitamin K-dependent glycoprotein synthesized in the liver. It circulates in the blood as an inactive zymogene at a concentration of 4 μg/ml. Its activation into the serine-protease like enzyme, activated protein C (aPC), is catalyzed by thrombin when it is bound to the endothelial

proteoglycan thrombomodulin.[21] Protein C and S deficiencies have been linked to an increased risk of miscarriage. For example, a study examined the effect of thrombo prophylaxis on the reduction of pregnancy losses. They found that women who received low-molecular-weight heparin treatment for deficiency of Protein C and S had a significantly lower miscarriage rate than those who did not receive the treatment so the best recommendations are based on expert opinion suggesting that Protein C and Protein S deficiencies may be a contributory factor of miscarriage. All women with a history of thrombo embolism who are planning pregnancy should be tested for inherited thrombophilias. In addition, women with a history of fetal loss, abruption, severe preeclampsia, and severe intrauterine growth restriction should also be tested. It is not yet clear whether patients with a history of recurrent early pregnancy losses at <10 weeks' gestation should be tested.[22]

**Antithrombin III deficiencies**

Antithrombin is a potent inhibitor of the reactions of the coagulation cascade. Although the name, antithrombin, implies that it works only on thrombin, it actually serves to inhibit virtually all of the coagulation enzymes to at least some extent. The primary enzymes it inhibits are factor Xa, factor IXa and thrombin (factor IIa). It also has inhibitory actions on factor XIIa, factor XIa and the complex of factor VIIa and tissue factor. Its ability to limit coagulation through multiple interactions makes it one of the primary natural anticoagulant proteins. Its numerous interactions are depicted on the above figure.[23] Antithrombin acts as a relatively inefficient inhibitor on its own. However, when it is able to bind with heparin, the speed with which the reaction that causes inhibition occurs is greatly accelerated; this makes the antithrombin-heparin complex a vital component of coagulation. This interaction is also the basis for the use of heparin and low-molecular-weight heparins as medications to produce anticoagulation. There are two primary types of antithrombin deficiency: type I and type II. Type I antithrombin deficiency is characterized by an inadequate amount of normal antithrombin present. In this case, there is simply not enough antithrombin present to inactivate the coagulation factors. In type II antithrombin deficiency, the amount of antithrombin present is normal, but it does not function properly and is thus unable to carry out its normal functions. In many cases, the antithrombin in type I deficiencies has a problem binding to heparin, although there have been multiple other changes to the antithrombin molecule described.[24]

The clinical relevance of a distinction between antithrombin I and antithrombin II deficiency lies in the higher risk of thrombosis associated with the type I variety. Antithrombin III is the most important inhibitor of thrombin, factor Xa, IXa and XII a. Antithrombin III deficiency results from the decrease in the concentration or the function of antithrombin III.[25]

**Plasminogen Activator Inhibitor 1 (PAI1)**

Plasminogen activator inhibitor-1 is the principal inhibitor of tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), the activators of plasminogen and hence fibrinolysis. Plasminogen activator inhibitor 1 (PAI-1) inhibits plasminogen activators (u-PA and t-PA) by forming stable complexes endocytosed via a low-density lipoprotein receptor super family member-dependent mechanism. PAI-1 circulates actively in plasma and latently in platelets but is also secreted and deposited into the matrix by several cells, where it participates in tissue repair processes. Endothelial PAI-1 expression is modulated by a 4G/5G polymorphism in the PAI-1 promoter, which is 675 bp upstream from the start site of transcription. Angiotensin II plasma levels also influence PAI-1 expression. Homozygosity for the 4G allele of the PAI-1 gene increases the risk for pregnancies, predisposing to prematurity, intrauterine growth retardation, miscarriage and stillbirth.[26]

**Acquired thrombophilia**

Acquired thrombophilias are hypercoagulable states secondary to various aetiologies. In particular, during pregnancy the risks are exaggerated due to the underlying physiological changes. The most common acquired thrombophilia associated with RM is the antiphospholipid syndrome (APS). Antiphospholipid antibodies are auto antibodies against negatively charged phospholipids. APS is categorized as primary (where it occurs in isolation) and secondary.[27]

**Acquired hyperhomocystinemia**

Hyperhomocystinemia has been underlined as an emerging risk factor for several diseases such as arterial and/or venous thrombosis Hyperhomocystinemia may be acquired secondary to dietary and lifestyle factors such as a reduced intake of folate, vitamin B6 or vitamin B12, excessive caffeine consumption and excessive coffee intake. The acquired form of hyperhomocystinemia may also result from certain medical conditions such as hypothyroidism or renal impairment. Inherited and acquired conditions have been involved to explain pathophysilogy as gene polymorphism.[28] The Homocysteine Lowering Trial Collaboration has suggested that endothelial dysfunction, alteration of platelet reactivity and

disruption of prostacyclin pathways, may be some of the mechanisms responsible for the reported venous thrombosis risk as well as the theoretical risk of pregnancy loss. A meta-analysis of ten studies concluded that acquired hyperhomocystinemia is a risk factor for recurrent pregnancy loss.[29]

**Acquired activated protein C resistance**

APCR is the most prevalent risk factor for thrombosis. The presence of the factor V Leiden mutation produces a protein that is intrinsically resistant to activated protein C, causing the pathological phenotype. The pathophysilogy underlying APCR not caused by the FVL mutation is still not completely understood. In different studies, it has been suggested that acquired factors might be the cause of APCR in the absence of FV Leiden. A number of coagulation factors can affect the activated partial thromboplastin time (aPTT). Previous literature suggested a possible positive correlation between levels of factors V, VIII and IX and acquired APCR. Protein S and protein C, levels can (or may) affect acquired APCR.[30]

**Antiphospholipid syndromes**

Antiphospholipid syndrome or antiphospholipid antibody syndrome (APS or APLS), or often also Hughes syndrome, is an autoimmune, hypercoagulable state caused by antiphospholipid antibodies. Antiphospholipid syndrome is the most important treatable cause of recurrent miscarriage. Anti phospholipid antibodies are a family of about 20 antibodies that are directed against phospholipid binding plasma proteins. Evidence for pregnancy loss having a thrombotic basis is based mostly in the association between anti-phospholipid (aPL) antibodies and RPL.[31]

Antiphospholipid syndrome can be primary or secondary. Primary antiphospholipid syndrome occurs in the absence of any other related disease. Secondary antiphospholipid syndrome occurs with other autoimmune diseases, such as systemic lupus erythematosus (SLE). In rare cases, APS leads to rapid organ failure due to generalized thrombosis; this is termed "catastrophic antiphospholipid syndrome (CAPS) and is associated with a high risk of death. They include lupus anticoagulant and anti cardiolipin antibodies. Antiphospholipid syndrome was originally defined as the association between antiphospholipid antibodies and recurrent miscarriage, thrombosis, or thrombocytopenia ,anti-phospholipid antibody syndrome is characterized by the presence of aPL, anti-lupus coagulant, anti-cardiolipin, and/or anti-beta-2-glycoprotein I antibodies that bind to negatively charged phospholipids on the membranes of endothelial cells, monocytes, and platelets.[32] Obstetric complications are

the other hallmark of anti- phospholipid syndrome. The risk of thrombosis among women with antiphospholipid antibodies may be increased. Thrombosis is presumed to cause many of the pregnancy complications associated with APS. The most common obstetric manifestation of this syndrome is recurrent miscarriage. Recurrent miscarriage occurs in about 1% of the general population attempting to have children. About 10-15% of women with recurrent miscarriage are diagnosed with antiphospholipid syndrome.[33]

## CONCLUSION

Thrombophilia either inheritance or acquired has been shown to be a major cause of recurrent pregnancy loss, patients with recurrent fetal loss should be evaluated for clotting disorders, even in the absence of clinical signs because there were some studies concluded that many positive hemophilic causative finding without any clinical signs. This evaluation may be useful in the Improvement of gynecological care of women with recurrent pregnancy loss and accurate knowledge of all significant complications in these women regarding thrombophilia and formulate a plan to diagnosis and treatment of these conditions.

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