The role of Inherited Blood Coagulation Disorders in Recurrent Miscarriage Syndrome

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Abstract

Pregnancy is a complicated physiological process that might lead to negative outcomes and could threaten the women`s life or the fetus. Miscarriage is a common occurrence in the life cycle of the woman. Exactly how common this experience is not known exactly. Current literature suggests that the cause of RM is only identifiable in up to 40%-50% of cases. Improvement of pregnancy outcome is considered as an important area of action for those concerned with the improvement of women's health and pregnancy outcome. Exploring the relation between blood coagulation mutations with recurrent miscarriages is a challenge. This is due to the fact that recurrent miscarriages are with multiple etiologies, where genetic factors are considered one of those etiologies. Advances technology in molecular genetics provides an accurate and reliable tool to precisely study the genetic abnormalities associated with many diseases. Several studies identified inherited blood coagulation disorders as the principal cause of recurrent miscarriage syndrome. In this review we briefly address the role of inherited blood coagulation disorders in pregnancy and conclude that patients with recurrent miscarriage should be evaluated for clotting disorders, even in the absence of clinical signs because there were some studies concluded that many positive hemophilic causatives 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 coagulation disorders and formulate a plan to diagnosis and treatment of these conditions.

Keywords: Recurrent Miscarriage, Blood Coagulation, Pregnancy

Introduction:

Recurrent miscarriage (RM), also known as recurrent pregnancy loss, is a distressing condition affecting around 1% of couples trying to conceive. It can be very frustrating for both clinicians and patients as, despite intensive workup, no clear underlying pathology is forthcoming in at least 50% of couples [1]. Normal pregnancy is characterized by profound changes in almost every organ system to accommodate the growing and developing fetoplacental unit. The major hematologic changes during pregnancy include expanded plasma volume, physiologic anemia, mild neutrophilia in some individuals, and a mildly prothrombotic state or thrombophilia [2]. Thrombophilia or prothrombotic state mechanism is not completely understood. The various theories proposed to explain this hypercoagulable state includes a hyper-estrogenic effect during pregnancy, hemodilution, and unknown placental factors [3]. 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 [4]. Thrombophilias have been implicated in a variety of obstetrical complications including preeclampsia (PE), intrauterine growth restriction (IUGR), placental abruption, and fetal loss [5]. Women with inherited bleeding disorders face hemostatic challenges during various stages of pregnancy. Women who are carriers may have abnormally low factor levels and be at risk as well. Bleeding may occur at the time of delivery and postpartum, but the patient may also be at risk following spontaneous pregnancy loss, during diagnostic procedures, and during termination of pregnancy [6]. This review will discuss the various inherited blood coagulation etiologies of RMS, and their pathophysiology.

Change of blood coagulation during pregnancy:

The function of the coagulation pathway is to keep hemostasis, which is the blockage of a bleeding or hemorrhage. Primary hemostasis is an aggregation of platelets forming a plug at the damaged site of exposed endothelial cells. Secondary hemostasis includes the two main coagulation pathways, intrinsic and extrinsic, that meet up at a point to form the common pathway. The common pathway ultimately activates fibrinogen into fibrin [7]. normal pregnancy is associated with major changes in many aspects of hemostasis all contributing to maintain placental function during pregnancy and to prevent excessive bleeding in delivery. Most changes in blood coagulation and fibrinolysis create a state of hypercoagulability. This phenomenon protects the woman from hemorrhage during delivery but predisposes her to thromboembolism both during pregnancy and in puerperium. The changes in the coagulation system in normal pregnancy are consistent with a continuing low-grade process of intravascular coagulation [8] .These include increases in a number of clotting factors (I, II, VII, VIII, IX and XII), a decrease in protein S levels and inhibition of fibrinolysis. As gestation progresses, there is also a significant fall in the activity of activated protein C, an important anticoagulant. While these physiological changes may be important for minimizing intrapartum blood loss, they entail an increased risk of thromboembolism during pregnancy and the post-partum period [9].

Inherited Blood Clotting Disorders in Recurrent Miscarriage Syndrome:

Inherited thrombophilia or blood clotting disorders 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 [5]. The most common inherited blood coagulation disorders are deficiencies of

antithrombin III, protein C and protein S, Factor V Leiden mutation, and prothrombin gene mutation (G20210A).

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. 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. If an individual has too much prothrombin, blood clots may form when they shouldn't [10]. 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 [11,12]. 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 [13]. 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 [14]. Higher incidence of inherited thrombophilia factor prothrombin G20210A mutation has been the focus of some studies in women with RM and suggest that the prothrombin G20210A mutation, may be an unrecognized cause of RMS [15,16,17].

Factor V Leiden G1691A 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 [18]. Factor V Leiden mutation is a result of an amino acid substitution of glutamine for Arginine at amino acid position 506 in the factor V molecule. During normal clotting activated protein C (APC) inactivates factor Va and VIIIa by cleavage at specific sites. In the presence of the mutation in factor V, the cleavage of this factor is deprived, leading to enhanced thrombin generation and hence increased clot formation [19]. Factor V mutation is 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. This may lead to placenta abruption and consequently results in miscarriage heterozygotes have a three to five times increased risk of thrombosis [20]. Women with this mutation are two to three times more likely to have multiple (recurrent) miscarriages or a pregnancy loss during the second or third trimester. Some research suggests that the factor V Leiden mutation may also increase the risk of other complications during pregnancy, including pregnancy-induced high blood pressure (preeclampsia), slow fetal growth, and early separation of the placenta from the uterine wall (placental abruption) .However, the association between the factor V Leiden mutation and these complications has not been confirmed. Most women with factor V Leiden thrombophilia have normal pregnancies and Homozygotes are much less common but have a much higher thrombotic risk, around eight times increased risk [21]. The association between the FVL mutation and RPL seems stronger for non-recurrent second-trimester pregnancy loss compared with recurrent early pregnancy loss [22]. Factor V Leiden mutation is the most common hypercoagulable disorder occurring in 5% of the white population. This mutation leads to a form of factor V that when activated to factor Va is resistant to degradation by activated protein C. There is increased procoagulants activity and therefore increased risk of Thromboembolism [23]. FVL according to epidemiology is present in around 5% of Caucasians and It is rare or absent in people of black African, Far East Asian, native Australian and native American origin and The chance of developing an abnormal blood clot depends on whether a person has one or two copies of the factor V Leiden mutation in each cell. People who inherit two copies of the mutation, one from each parent, have a higher risk of developing a clot than people who inherit one copy of the mutation [18].

Factor XII mutation:
Factor XII plasma protein is like other factors of the coagulation cascade a member of the serine proteases. The activated FXII (FXIIa)-induced activation of FXI is the crucial step in contact system-mediated coagulation activation. FXIIa is involved in the initiation of the coagulation cascade by cleaving prekallikrein. Kallikrein, in turn, cleaves the inactive zymogen factor XII to yield α-FXIIa and β-FXIIa. This latter process is accelerated by binding of the inactive zymogen FXII to a negatively charged surface via the N-terminal region of the protein. The coagulation cascade results in the formation of fibrin. Covalent cross-links between the fibrin strands by the action of FXIIIa finally stabilize the network [24]. Deficiency of coagulation factor XII is an autosomal recessive disorder whose clinical implications remain controversial. Factor XII is a serine protease that circulates in the plasma as an inactive zymogen and is involved in the initiation of the coagulation cascade [25]. To date, few studies have analyzed coagulation factor XII activities in women with recurrent abortion. Some authors have found an association between severe factor XII deficiency and an increased risk for recurrent abortion, whereas other groups failed to show this association [26]. Some studies find that, factor XII deficiency is strongly associated with primary recurrent abortion, and women with secondary recurrent abortion show a tendency toward factor XII deficiency [27,28,29].

Plasminogen Activator Inhibitor 1 (PAI1):
Fibrinolysis is the resulting of interactions among multiple plasminogen activators and inhibitors constituting the enzymatic cascade ultimately leading to the degradation of fibrin. The plasminogen activator system plays a key role in a wide range of physiological and pathological processes, including coagulation, fibrinolysis, inflammation, wound healing, and malignancy [30]. 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 [31].

Antithrombin III deficiencies:

Antithrombin III (ATIII) is a nonvitamin K-dependent protease that inhibits coagulation by neutralizing the enzymatic activity of thrombin (factors IIa, IXa, Xa). Antithrombin III activity is markedly potentiated by heparin, the principal mechanism by which both heparin and low–molecular-weight heparin result in anticoagulation [32]. 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 [33]. 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 [34]. 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.

Protein C and Protein S deficiencies:

The protein C (PC) pathway, with its cofactor protein S (PS), is an important natural antithrombotic mechanism. Both PC and PS deficiencies have been implicated in thrombophilia. The molecular basis for hereditary PC and PS deficiencies is highly heterogeneous, with a large spectrum of mutations that have various effects on the expression of the relevant allele. A small subset of patients who are homozygous or compound heterozygous for a PC gene mutation have severe thrombotic complications at birth, whereas onset occurs later in the other cases [35]. 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 [36]. Protein S is a vitamin K-dependent, single-chain glycoprotein, which is synthesized in the liver and vascular endothelium, and acts mainly as a cofactor to aPC in the inactivation of FVIIa and FVa. Protein S is the principle cofactor of activated protein C , and deficiency states mimic protein C deficiency with increased fibrin

formation Protein . Bind directly to inhibit factors Va, VIIIa, and Xa. Proteins exists in two distinct forms in plasma the free form accounts for 35 to 40% of total protein S , whereas the remainder is found in a form bound to C4b binding protein. Only the free protein S can serve as a cofactor for protein. The plasma level of protein S depends upon age, sex, lipid levels, estrogen, oral anticoagulant usage and the presence of acute thrombosis. In the plasma, around 60% of circulating protein S is bound to C4b binding protein, and only free protein S can function as a cofactor to aPC. Heritable protein S deficiency is transmitted as an autosomal trait. Those with heterozygous deficiency are at increased risk of venous thrombotic events (VTE), as well as warfarin-induced skin necrosis [36]. Protein S plays a role in inhibition of the clotting cascade. Protein S and C inactivate factors VIIIa and Va, required cofactors for factors IXa and Xa. This is important because the most important natural inhibitor of clotting, the tissue factor pathway inhibitor, can be short circuited by factor IXa; so inhibition of the clotting cascade requires inhibition of factors IXa and Xa. This is achieved with the complex of activated protein C and protein S [37]. Certain conditions, such as pregnancy, inflammation, and surgical stress, lead to increased levels of the complement 4b-binding protein, which binds to protein S, and thereby decrease protein S activity. In addition, pregnancy is a thrombogenic state because of other alterations in the coagulation pathway. There is a 20% to 200% increase in levels of fibrinogen and some clotting factors. At the same time, the tissue factor pathway inhibitor increases only minimally, whereas antithrombin and protein C levels remain constant. Protein S deficiency is an autosomal dominant mutation that confers a modest risk of thrombo embolism 5% to 20% risk during pregnancy and the postpartum period. The risk of miscarriage does not seem to be increased with a deficiency of protein S or protein C. However, there may be an increased risk of fetal loss later in pregnancy, severe preeclampsia, abruption placenta, and fetal growth restriction with protein C or S deficiency. There are no randomized prospective trials to show the efficacy of different anticoagulation regimens in affected patients [38]. Many studies have tried to address this issue and there is still controversy regarding the importance of thrombophilia in fetal loss. Association is often difficult to uncover because of inherent study design issues in the pregnant population [39]. Some previous study results conducted to show association of these factors and RMS reported that the different prevalence of these mutations and polymorphism in different populations depending on ethnic background could explain these differences [40].

Conclusion:

Inheritance blood coagulation factors has been shown to be a major cause of recurrent miscarriage syndrome, patients with recurrent miscarriage should be evaluated for clotting disorders, even in the absence of clinical signs because there were some studies concluded that many positive hemophilic causatives 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 coagulation disorders and formulate a plan to diagnosis and treatment of these conditions.

Disclosure
The author report no conflicts of interest in this work

References:

1. Homer, H. A. (2019). Modern management of recurrent miscarriage. Australian and New Zealand Journal of Obstetrics and Gynaecology, 59(1), 36-44.
2. Bauer, K. A., & Tirnauer, J. S. (2018). Maternal adaptations to pregnancy: hematologic changes. UpToDate.

3. Reddy, R. R. N., Mutreja, D., Moorchung, N., & Mukhopadhyay, I. (2019). Recurrent pregnancy loss: can factor V Leiden mutations be a cause. Obstetrics & gynecology science, 62(3), 179-182.
4. Khan, S., & Dickerman, J. D. (2006). Hereditary thrombophilia. Thrombosis journal, 4(1), 15.
5. Liatsikos, S. A., Tsikouras, P., Manav, B., Csorba, R., von Tempelhoff, G. F., & Galazios, G. (2016). Inherited thrombophilia and reproductive disorders. Journal of the Turkish German Gynecological Association, 17(1), 45.
6. Gernsheimer, T. B. (2016). Congenital and acquired bleeding disorders in pregnancy. ASH Education Program Book, 2016(1), 232-235.
7. Chaudhry, R., & Babiker, H. M. (2018). Physiology, Coagulation Pathways. In StatPearls [Internet]. StatPearls Publishing.
8. Prisco, D. O. M. E. N. I. C. O., Ciuti, G. A. B. R. I. E. L. E., & Falciani, M. I. C. H. E. L. A. (2005). Hemostatic changes in normal pregnancy. Haematologica reports, 1(10), 1-5.
9. Bremme, K. A. (2003). Haemostatic changes in pregnancy. Best practice & research Clinical haematology, 16(2), 153-168.
10. Varga, E. A., & Moll, S. (2004). Prothrombin 20210 mutation (factor II mutation). Circulation, 110(3), e15-e18.
11. Khan, S., & Dickerman, J. D. (2006). Hereditary thrombophilia. Thrombosis journal, 4(1), 15.
12. Babker, A. M. A. A. A., & Gameel, F. E. M. H. (2015). Molecular Characterization of Prothrombin G20210A gene Mutations In pregnant Sudanese women with spontaneous recurrent abortions. Rawal Medical Journal, 40(2), 207-209.
13. Jadaon, M. M. (2011). Epidemiology of prothrombin G20210A mutation in the Mediterranean region. Mediterranean journal of hematology and infectious diseases, 3(1).
14. Attia, F. M., Mikhailidis, D. P., & Reffat, S. A. (2009). Prothrombin gene G20210A mutation in acute deep venous thrombosis patients with poor response to warfarin therapy. The open cardiovascular medicine journal, 3, 147.
15. Foka, Z. J., Lambropoulos, A. F., Saravelos, H., Karas, G. B., Karavida, A., Agorastos, T., ... & Kotsis, A. (2000). Factor V Leiden and prothrombin G20210A mutations, but not methylenetetrahydrofolate reductase C677T, are associated with recurrent miscarriages. Human Reproduction, 15(2), 458-462.
16. Poort, S. R., Rosendaal, F. R., Reitsma, P. H., & Bertina, R. M. (1996). A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood, 88(10), 3698-3703.
17. Kardi, M. T., Yousefian, E., Allahveisi, A., & Alaee, S. (2018). Association of factor V Leiden and prothrombin G20210A polymorphisms in women with recurrent pregnancy loss in Isfahan province, Iran. International journal of preventive medicine, 9.
18. van Mens, T. E., Levi, M., & Middeldorp, S. (2013). Evolution of factor V Leiden. Thrombosis and haemostasis, 110(07), 23-30.
19. Babker, A. M. A. A. A., & Gameel, F. E. M. H. (2014). The frequency of factor V leiden mutation among Sudanese pregnant women with recurrent miscarriage. Journal of American Science, 10(9).
20. Procházka, M., Happach, C., Maršál, K., Dahlbäck, B., & Lindqvist, P. G. (2003). Factor V Leiden in pregnancies complicated by placental abruption. BJOG: An International Journal of Obstetrics & Gynaecology, 110(5), 462-466.
21. van Vlijmen, E. F., Veeger, N. J., Middeldorp, S., Hamulyák, K., Prins, M. H., Büller, H. R., & Meijer, K. (2011). Thrombotic risk during oral contraceptive use and pregnancy in women with factor V Leiden or prothrombin mutation: a rational approach to contraception. Blood, 118(8), 2055-2061.
22. Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GD, et,al.(2006) .Thrombophilia in pregnancy: a systematic review. Br J Haematol 132:171-196.
23. Kujovich JL (2011). Factor V Leiden thrombophilia. Genet Med. Jan;13(1):1-16.
24. Schloesser, M., Zeerleder, S., Lutze, G., Halbmayer, W. M., Hofferbert, S., Hinney, B., ... & Köhler, M. (1997). Mutations in the human factor XII gene. Blood, 90(10), 3967-3977.
25. Citarella, F., Ravon, D. M., Pascucci, B., Felici, A., Fantoni, A., & Hack, C. E. (1996). Structure/function analysis of human factor XII using recombinant deletion mutants: evidence for an additional region involved in the binding to negatively charged surfaces. European journal of biochemistry, 238(1), 240-249.
26. Pauer, H.U., Burfeind, P., Köstering, H., Emons, G. and Hinney, B., 2003. Factor XII deficiency is strongly associated with primary recurrent abortions. Fertility and sterility, 80(3), pp.590-594.
27. Pauer, H.U., Burfeind, P., Köstering, H., Emons, G. and Hinney, B., 2003. Factor XII deficiency is strongly associated with primary recurrent abortions. Fertility and Sterility, 3(80), pp.590-594.
28. Mariano, M. L., Yadira, P., Ana, A., Manuel, L., & Jesús, L. G. J. (2011). Coagulation Factor XII Congenital Deficiency in Women with Recurrent Miscarriage. International Journal of Clinical Medicine, 2(04), 469.
29. Ozgu-Erdinc, A. S., Togrul, C., Aktulay, A., Buyukkagnici, U., Yapar Eyi, E. G., & Erkaya, S. (2014). Factor XII (Hageman) levels in women with recurrent pregnancy loss. Journal of pregnancy, 2014.
30. Cesari, M., Pahor, M. and Incalzi, R.A., 2010. Plasminogen activator inhibitor-1 (PAI-1): a key factor linking fibrinolysis and age-related subclinical and clinical conditions. Cardiovascular therapeutics, 28(5), pp.e72-e91.
31. Buchholz T, Lohse P, Rogenhofer N, Kosian E, Pihusch R, Thaler CJ. (2003). Polymorphisms in the ACE and PAI-1 genes are associated with recurrent spontaneous miscarriages Hum Reprod . ;18:2473-2477.
32. Smith, S.A. and Morrissey, J.H., 2008. Heparin is procoagulant in the absence of antithrombin. Thrombosis and haemostasis, 100(07), pp.160-162.
33. Hyers TM.,(2001). Antithrombotic therapy for venous thromboembolic disease. Chest, 119(1 Suppl): p. 176S-193S.
34. Brenner B, HoffmanR, BlumenfeldZ,Weiner Z, Younis JS (2000). Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. Thromb Haemost.83(5): p. 693-7.
35. Dixit, A., Kannan, M., Mahapatra, M., Choudhry, V. P., & Saxena, R. (2006). Roles of protein C, protein S, and antithrombin III in acute leukemia. American journal of hematology, 81(3), 171-174.
36. Dahlback B (2008). Advances in understanding pathogenic mechanisms of thrombophilic disorders. Blood. Jul 1.112(1):19-27.
37. Abu-Heija, A. (2014). Thrombophilia and Recurrent Pregnancy Loss: Is heparin still the drug of choice?. Sultan Qaboos University Medical Journal, 14(1), e26.
38. Bates, S. M., Greer, I. A., Middeldorp, S., Veenstra, D. L., Prabulos, A. M., & Vandvik, P. O. (2012). VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(2), e691S-e736S.
39. McNamee, K., Dawood, F., & Farquharson, R. (2012). Recurrent miscarriage and thrombophilia: an update. Current Opinion in Obstetrics and Gynecology, 24(4), 229-234.
40. Battinelli, E. M., Marshall, A., & Connors, J. M. (2013). The role of thrombophilia in pregnancy. Thrombosis, 2013.
41. Babker, A. M. A. A. A., & Gameel, F. E. M. H. (2016). Methylenetetrahydrofolate reductase c677t polymorphism in

Sudanese women with recurrent spontaneous abortions. Kuwait Medical Journal, 48(2), 100-104.