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Hereditary Thrombophilia and Recurrent Pregnancy Loss

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Abstract: The challenging nature of recurrent pregnancy loss (RPL) is multifactorial, but largely begins with determining who meets diagnostic criteria for RPL as definitions vary and frequently change. Many patients seek obstetrical intervention after losses, even if they do not meet the criteria for RPL, and even those strictly meeting criteria often present a conundrum as to the etiology of their condition. The contribution of hereditary thrombophilia to RPL, the impact of each disorder on the clotting cascade, available evidence regarding pregnancy outcomes, and current recommendations for evaluation and treatment is presented.
Key words: recurrent pregnancy loss, hereditary thrombophilia, clotting cascade

Introduction

Management of patients with recurrent pregnancy loss (RPL) can be an emotional and frustrating task for the obstetrician. The challenging nature of this clinical problem is multifactorial, but largely begins with determining who meets diagnostic criteria for RPL as definitions vary and frequently change. Commonly used definitions include the following:

- Two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination.[1]
- Three consecutive pregnancy losses, which are not required to be intrauterine.[2]

A retrospective cohort study of 587 women who had 3 or more consecutive pregnancy losses before 12 weeks' gestation demonstrated that biochemical pregnancies and pregnancies of unknown location have a similarly negative impact on future live birth as intrauterine pregnancy losses.[3] Many patients seek obstetrical intervention after losses, even if they do not meet the above criteria for RPL, and even those strictly meeting criteria often

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present a conundrum as to the etiology of their condition. Approximately 15% of pregnant women will experience a sporadic loss of a clinically recognized pregnancy, 2% will have 2 consecutive pregnancy losses, and 1% or less will have 3 consecutive losses.[4] Often, the cause of RPL cannot be determined; no discrete diagnosis can be made in upward of 50% of patients.[5] RPL is often multifactorial; an extensive discussion of discrete causes can be found elsewhere. In this chapter, we will focus on the contribution of hereditary thrombophilia to RPL, including a review of pertinent inherited thrombophilias, the impact of each disorder on the clotting cascade, available evidence regarding pregnancy outcomes, and current recommendations for evaluation and treatment.

Pregnancy: A Prothrombotic State

Pregnancy poses significant systemic hemostatic challenges, even in the healthiest of patients. The physiology of pregnancy is one primed for thrombosis. All of Virchow's classic antecedents of thrombosis are present and evolve as pregnancy continues. The hormonal changes of pregnancy lead to pooling of venous return in the lower extremities, with venous stasis resulting from vasodilation. The gravid uterus further promotes stasis within the lower extremities. Endothelial injury is a key component of implantation, and delivery represents profound endothelial damage. In combination with physiological risks, many of the procoagulant factors of the clotting cascade progressively increase during pregnancy including factor II, VII, VIII, and X. Fibrinolysis is also suppressed through a measurable decrease in protein S and resistance to activated protein C.[6]

As a result, pregnancy can be referred to as a prothrombotic state with the high-volume, high-flow, low-resistance uteroplacental circulation necessitating this enhanced hemostatic response.[7] A successful pregnancy is a complex balance of the risks of hypercoagulability and hemorrhage from the moment of implantation to the time of delivery. Hemorrhage must be avoided during implantation as cytotrophoblasts invade the maternal decidual vessels to remodel the architecture of the maternal spiral arteries. The uterine decidual layer plays a crucial role in the prevention of hemorrhage during embryo implantation, placentation, and the third stage of labor. As with the paradoxical nature of hemostasis in pregnancy, decidual tissue factor can also promote the intense hypofibrinogenemia and disseminated intravascular coagulation observed in placental abruption and the coagulopathy seen in amniotic fluid embolism.[8] Associated perils also include increased risk for thrombotic complications, a risk further increased in women with thrombophilias. Venous thromboembolism (VTE) and associated complications remain a leading cause of maternal morbidity and mortality accounting for an estimated 9.3% of maternal deaths in the United States from 2006 to 2010.[6] But with risks, there are crucial benefits as this hypercoagulable balance drives a rapid transition from 600 to 700 mL/minute of uterine blood flow at term to appropriate postpartum bleeding in a matter of minutes during delivery and puerperium. Disruption in this tenuous balance can inhibit implantation, initiate miscarriage, drive pathologic placentation, or result in hemorrhage.

Inherited Thrombophilias in Pregnancy

Inherited dysfunction of the coagulation cascade results in a compounding effect of the hypercoagulable state of pregnancy. By affecting the quantity and/or function of certain coagulation factors, inherited thrombophilias can disturb the coagulation system. There is little dispute

regarding the relationship between inherited thrombophilia and thrombotic events including deep vein thrombosis and pulmonary embolism. Controversy remains regarding the connection between inherited thrombophilia and adverse pregnancy outcomes, including spontaneous abortion, fetal loss, preeclampsia, fetal growth restriction, and placental abruption.[8] Given the emotionally charged nature of these complications, inherited thrombophilias continue to spur curiosity, with meta-analyses consistently finding data to support varying degrees of association between thrombophilias and pregnancy loss. Below we will review the most common inherited thrombophilias and available data regarding their association with adverse pregnancy outcomes.

Factor V Leiden (FVL)

The FVL carrier prevalence is approximately 5% to 9% among whites of European decent, making it the most common inherited thrombophilia.[8,9] The mutation is virtually absent in African, Chinese, Japanese, and other Asian populations; however, it is present in about 3% of African Americans who are not recent immigrants. The rate of homozygosity is approximately 1% among those with the gene mutation, resulting in a more severe phenotype. The condition results from a point mutation on chromosome 1q23, driving the substitution of arginine by glutamine at position 506 on the subsequent protein.[5] This single substitution creates a distorted protein C cleavage site, making factor Va resistant to cleavage and deactivation. In its intended state, factor V is activated by thrombin to factor Va. Factor Va is then responsible for the conversion of prothrombin to thrombin. In the reverse fibrinolytic cascade, factor Va is cleaved by activated protein C and provides negative feedback for factor VIII. In those affected by FVL, the distorted cleavage site results in a factor Va that is resistant to downregulation by protein C, and unable to modulate the activity of factor VIII (Fig. 1).

In regard to recurrent fetal loss, data surrounding FVL is the most robust compared with other inherited thrombophilias. In a meta-analysis that included 31 case-control, cohort, and cross-sectional studies, Rey and colleagues determined an association between FVL and RPL before 13 weeks (OR = 2.01; 95% CI, 1.13-3.58). Investigators also found a similar association when evaluating studies covering all gestational ages in which other causes for fetal loss were excluded (OR = 3.04; 95% CI, 2.16-4.3). The meta-analysis only included 1 study limited to recurrent fetal losses at > 22 weeks, which found an OR = 7.83 (95% CI, 2.83-21.67).[10] Interestingly, a cohort study by Roqué et al[11] determined FVL to have protective benefits from recurrent fetal loss starting before 10 weeks of gestation (OR = 0.23; 95% CI, 0.07-0.77) but not from weeks 10 to 14 (OR = 1.07; 95% CI, 0.46-2.50). Rodger and colleagues provide the largest prospective data set evaluating FVL and fetal loss in a 2010 meta-analysis of 10 prospective cohort studies. Although RPLs were not evaluated, they found a small but statistically significant association between FVL and pregnancy loss at all gestational ages (OR = 1.52; 95% CI, 1.06-2.19).[12] Overall, FVL appears to pose a small increased risk of spontaneous abortion and fetal loss. Limited data regarding RPL and FVL also suggest a modest association.

Prothrombin Gene Mutation (PGM)

The prothrombin G20210A mutation results from a single guanine to adenine nucleotide point mutation in the untranslated 3′ region of the gene coding for prothrombin. This alteration results in increased translation and elevated circulating prothrombin levels.[8] The prevalence of

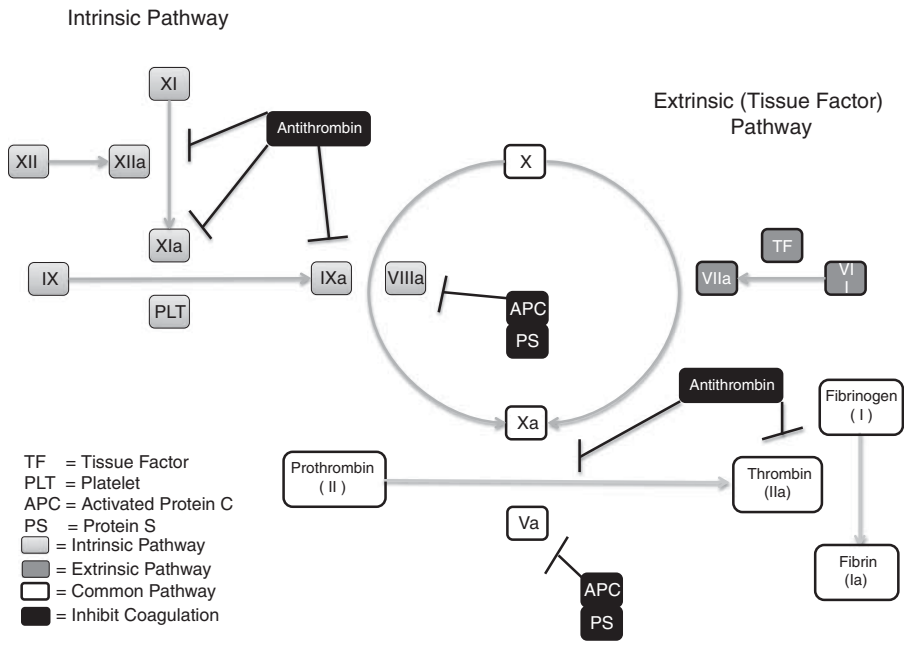

FIGURE 1. Important factors of the coagulation system.

the mutation is between 2% and 4% among European whites; it is less common among women of African and Asian descent.[9,13]

Although the connection between PGM and VTE in pregnancy is clear, data regarding the impact of the PGM on early and RPL is uncertain. On the basis of Rey's meta-analysis of 31 case-control, cohort, and cross-sectional studies, as outlined above, the mutation was linked to recurrent first trimester loss (OR = 2.32; 95% CI, 1.12-4.79) and recurrent fetal loss before 25 weeks (OR = 2.56, 95% CI, 1.04-6.29). There also was a significant association with nonrecurrent fetal loss when studies across all gestational were included (OR = 2.05; 95% CI, 1.18-3.54).[10] In contrast, a systemic review that included 4 prospective studies addressing PGM and fetal loss at all gestational ages failed to find an association (OR = 1.13; 95% CI, 0.64-2.01).[12] Reviews of these data highlight the limitations and inherent bias of the studies included. Overall, although PGM is a common heritable risk factor for thrombosis in pregnancy, data connecting this thrombophilia and pregnancy loss, recurrent or not, are contradictory and definitive conclusions cannot be made based on available information.

Protein C Deficiency

Although FVL and the prothrombin gene mutation G20210A often result in similar or predictable phenotypes, protein C deficiency has been linked to >160 distinct mutations resulting in variable phenotypes. The prevalence of protein C mutation is estimated at 0.2% to 0.3% when determined by a functional assay with cutoff between 50% and 60%.[8,13] The mutation may be more common among those of Asian or African descent.[9] Protein C deficiency is inherited in an autosomal dominant pattern, with deficiency described by 2 distinct subtypes, Type I and Type II. Type I is more common and results in both a decreased amount and activity of protein C with extensive heterogeneity in

phenotype. Type II results in a normal level of protein C, but with decreased functional activity. Protein C is a vitamin K-dependent protein produced by the liver. When functional, it circulates as a zymogen and participates in anticoagulation following activation to become a serine protease, termed activated protein C. This activation can be mediated by thrombin, or most efficiently when thrombin is bound to endothelial thrombomodulin. When activated, protein C inactivates factor Va and VIIIa. Downstream, this effect prevents activation of factor X and thrombin generation. The effect of protein C is enhanced by protein S, which will be discussed in greater detail below.

Protein C deficiency has not been clearly linked to fetal loss or to RPL. The European Prospective Cohort on Thrombophilia (EPCOT) study evaluated 843 women with varied thrombophilias and determined the OR for protein C deficiency and fetal loss at any gestational age to be 1.4 (95% CI, 0.9-2.2), and 2.3 (95% CI, 0.6-8.3) for stillbirth defined as fetal loss > 28 weeks' gestation, both statistically nonsignificant findings.[14] Rey et al[10] found the risk of RPL across all gestational ages to be nonsignificant (OR = 1.57; 95% CI, 0.23-10.54), though the meta-analysis only included small retrospective case-control studies. Along the spectrum of maternal-fetal well-being, a rare fetal complication may result from homozygous or compound heterozygous protein C deficiency termed neonatal purpura fulminans. The condition is characterized by disseminated intravascular coagulation and hemorrhagic skin necrosis, caused by extremely low levels of protein C. Despite this rare condition, there remains no clear association between protein C deficiency and RPL.

Protein S Deficiency

Protein S is a vitamin K-dependent protein intimately involved in the protein C anticoagulation mechanism. Deficiency in protein S is caused by a silenced gene or a mutation that results in reduced free protein S antigen levels and activity. There are over 130 known mutations with variable expression.[8] Protein S deficiency is less common with an estimated prevalence of 0.03% to 0.13% among whites. However, true prevalence estimations may be limited by substantial variability in detection assays during pregnancy. For more reliable evaluation, screening is recommended outside of pregnancy, > 6 weeks postpartum and in the absence of hormonal contraception. Free protein S is significantly decreased in pregnancy. Levels decrease between the second and third trimester, from 38.9% ± 10.3% to 31.2% ± 7.4%.[15] When functioning, protein S accelerates protein C's effect on factor Va and VIIIa, with downstream suppression of thrombin formation. Protein S deficiency is divided into 3 major phenotypes. Type I has low levels of protein S antigen, free and total, and decreased function. Type II has normal free and total antigen, but with impaired function. Type III has normal total antigen values, but low free protein S and decreased activity level.

Although few data exist regarding protein S deficiency and RPL, some data regarding nonrecurrent fetal loss are available. Preston et al[14] failed to find an association between pregnancy loss and protein S (OR = 1.3; 95% CI, 0.8-2.1). Conversely, a systematic review indicated an association with stillbirth (defined as unexplained fetal loss over 20-wk gestation with no fetal abnormalities) with an OR = 16.2 (95% CI, 5.0-52.3), though it was limited by small study sizes.[16] Others studies have found similar findings.[10] Given limited data to date, definitive conclusions regarding the affect of protein S on RPL cannot be drawn and investigation continues.

Antithrombin Deficiency

Antithrombin deficiency was the first hereditary thrombophilia identified; it is also

the most thrombogenic. There are > 250 associated mutations serving to decrease gene transcription, leading to decreased antithrombin antigen levels and activity or normal antigen levels but decreased activity.[8] Inheritance patterns are autosomal dominant with variable penetrance. Prevalence of the mutation is estimated at 1 per 2500 patients, or a 0.02% to 1.15% among European whites. The prevalence may be higher in Asians with estimated prevalence of 2% to 5%.[9] Antithrombin is synthesized in the liver and endothelial cells; its primary mechanism of action is through an inhibitory effect on thrombin, working to prevent activated thrombin's conversion of fibrinogen to fibrin. Antithrombin also acts as an inhibitor of clotting factors IX, X, XI, XII and tissue-factor bound VIIa.[5] Similar to the thrombophilias outlined above, antithrombin deficiency is defined by subgroups. Type I is a quantitative dysfunction and Type II is a qualitative dysfunction. Type II is again further divided into subcategories; Type IIa is characterized by a defect in the reactive site of the protein, and the resulting phenotype is often more thrombogenic. Type IIb has a defect in the heparin-binding site, but the resulting phenotype is less thrombogenic. Type IIc includes both of the aforementioned defects.

Given the rarity of antithrombin deficiency, it is challenging to draw conclusions as to the thrombophilia's effect on pregnancy loss and related sequelae. The EPCOT study found a modest increase risk in early fetal loss, as defined by gestational age < 28 weeks (OR = 1.7, 95% CI, 1.0-2.8). They also found a significant association with nonrecurrent losses at all gestational ages (OR = 2.1; 95% CI, 1.2-3.6) and after 28 weeks (OR = 5.2; 95% CI, 1.5-18.1).[14] Meta-analyses found no association with fetal loss, recurrent or not, but studies were limited by small numbers and retrospective design.[10] In summary, data suggest an association between antithrombin deficiency and pregnancy loss, but a definitive causative relationship is not yet established.

Methylenetatrahydrofolate Reductase (MTHFR)

MTHFR is an enzyme involved in folate metabolism. MTHFR's role is to reduce 5,10 methylenetatrahydrofolate to 5-methyltetrahydrofolate. The resulting enzyme acts to reduce homocysteine to methionine. Homozygosity for a MTHFR mutation is the most common cause of hyperhomocysteinemia. Homozygosity of the MTHFR C677T and A1298C polymorphisms is present in 10% to 16% and 4% to 6% of all Europeans, respectively. The C677T allele has a carrier frequency from 7% in sub-Saharan Africans to 44% in Italians.[17] The activity of the resulting enzyme is thermolabile, and is therefore less active at temperatures > 37°C. Homozygotes for the C677T mutation demonstrate elevated plasma homocysteine when folate deficient, but normal levels when folate replete. The second mutation, A1298C, results in a more modest decrease in enzyme function. Despite the potential for decreased folate in individuals homozygous for these mutations, hyperhomocysteinemia is quite rare given common folate food fortification and diets rich in folate.

When homocysteinemia is present, it acts as a procoagulant. However, elevated homocysteine levels remain a weak risk factor for VTE.[8] Similarly, there does not seem to be connection between MTHFR and homocysteinemia with adverse pregnancy outcomes. At best, available data are inconsistent with 1 meta-analysis finding a small link to recurrent fetal losses < 16 weeks (OR = 2.7; 95% CI, 1.4-5.2).[18] A 2000 study evaluating the pregnancies of 5883 women and 14,492 pregnancies found some correlation between elevated homocysteine and stillbirth, but the correlation did not meet statistical significance.[19]

More recent work has not indicated a link between MTHFR homozygosity or elevated homocysteine with adverse pregnancy outcomes.

Other Adverse Pregnancy Outcomes

Although the focus of this chapter remains the impact of inherited thrombophilias on RPL, data suggest these conditions may impact ongoing pregnancies, both in terms of fetal and maternal health. The conditions outlined below are important causes of perinatal morbidity and they share pathophysiology with some cases of pregnancy loss.

PREECLAMPSIA

Preeclampsia remains an increasingly common, but poorly understood disease of pregnancy. Given the high degree of maternal morbidity and mortality, copious ongoing studies strive to understand risk factors for disease development as well as treatment. Although case-control studies suggest an association between FVL and preeclampsia, meta-analysis of prospective studies fail to show a significant relationship (OR = 1.23; 95% CI, 0.89-1.70).[12] Similar studies have been conducted among those with the PGM. A nested case-control cohort evaluation through the Danish National Birth Cohort found no association between PGM and preeclampsia with severe features (OR = 0.81; 95% CI, 0.29-2.30).[20] One meta-analyses suggest a connection between protein C and protein S deficiency and preeclampsia. However, studies remain few and small in participant numbers.[16] Although antithrombin deficiency has not been found to be a risk factor for preeclampsia, antithrombin is currently being evaluated as a therapy for preeclampsia. Antithrombin has both anticoagulant and anti-inflammatory properties, making it a plausible candidate for therapeutic intervention. Several smaller studies demonstrated success in prolonging pregnancies in early-onset severe preeclampsia with antithrombin treatment. Currently, there is a large multicenter double-blinded randomized controlled trial underway studying recombinant antithrombin therapy for severe preeclampsia between 23 and 30 weeks. Nonetheless, there has been no clear connection or causative relationship demonstrated between any of the inherited thrombophilias and preeclampsia.[21]

FETAL GROWTH RESTRICTION

Fetal growth restriction has links to numerous maternal, fetal, and placental conditions. Thus, a link between fetal growth restriction and inherited thrombophilia has been extensively studied. A meta-analysis that evaluated the relationship between fetal growth restriction, homozygous and heterozygous FVL, homozygous and heterozygous PGM, and MTHFR homozygosity found no relationship or a weak relationship between these entities and fetal growth restriction.[22]

PLACENTAL ABRUPTION

A consistent association between any inherited thrombophilia and placental abruption has not been demonstrated. This may be in part due to the relatively rare occurrence of placental abruption in combination with the rarity of diagnosed inherited thrombophilias, making it challenging to conduct well-designed studies in this area.

Who Should be Tested and Should Treatment be Considered?

When a patient experiences RPL, there is temptation to consider broad diagnostic testing in an effort to offer some explanation for this emotional outcome. However, given the clinical evidence to date, routine inherited thrombophilia screening is not recommended for those

TABLE 1. Association Between Hereditary Thrombophilias and Selected Pregnancy Complications

	Nonrecurrent Pregnancy Loss	Late Nonrecurrent Pregnancy Loss*	Recurrent First Trimester Loss†	Recurrent Pregnancy Loss† ‡
FVL	1.52 (1.06-2.19)[12‡]	2.06 (1.1-3.86)[23]	1.91 (1.01-3.61)[23]	3.04 (2.16-4.3)[10]
PGM	1.13 (0.64-2.01)[12‡]	2.66 (1.28-5.53)[23]	2.70 (1.37-5.34)[23]	2.05 (1.18-3.54)[10]
Protein C deficiency	1.4 (0.9-2.2)[14]	2.3 (0.6-8.3)[14]	N/A	1.57 (0.23-10.54)[10]
Protein S deficiency	1.3 (0.8-2.1)[14]	7.39 (1.28-42.83)[10]	N/A	14.72(0.99-218.01)[10]
Antithrombin deficiency	2.1 (1.2-3.6)[14]	5.2 (1.5-18.1)[14]	N/A	N/A

Data are odds ratio (95% confidence interval).

*Studies varied in definition of late from > 20 to > 28 weeks gestation.

† Meta-analysis data, studies varied in definition of recurrent to include ≥ 2 or ≥ 3 prior events.

‡ Meta-analysis data, gestational age range varied in individual studies, all gestational ages included.

FVL indicates factor V Leiden; PGM, prothrombin gene mutation.

experiencing RPL[8] (Table 1). In addition, routine screening among women with adverse pregnancy outcomes including preeclampsia, IUGR, and placental abruption is not recommended. In cases of stillbirth, evaluation for thrombophilia may be considered if the suspected etiology of the stillbirth includes a possible thrombotic event. Discussion of further evaluation of RPL, preeclampsia, IUGR, and placental abruption includes evaluation of acquired thrombophilia, which is discussed elsewhere.

There have been a number of small observational trials evaluating pharmacologic intervention among this population; however, comparison of outcomes is limited by study heterogeneity of inclusion and exclusion criteria, and treatment regimen, in addition to small sample size and resulting confounding error. The 2010 SPIN study assessed pregnancy outcomes among 294 women with at least 2 consecutive pregnancy losses in the United Kingdom and New Zealand. Women were randomized to receive enoxaparin versus low-dose aspirin, in addition to close pregnancy surveillance, in parallel to a control group receiving close pregnancy surveillance only in a multicenter randomized controlled trial. Of the 147 women receiving pharmacologic intervention, 32 (22%) experienced pregnancy loss as compared with 29 (20%) women receiving close pregnancy surveillance only, resulting in an OR of 0.91 (95% CI, 0.52-1.59).[24] Of note, this study evaluated women with unexplained RPL, and not those with concurrent inherited thrombophilia. A 2014 systematic review of 9 clinical trials among women with RPL (defined as 2 or more consecutive miscarriages) with or without concurrent inherited thrombophilia also evaluated the role of anticoagulation. Included trials were both randomized and quasi-randomized in nature, with interventions including unfractionated heparin, low–molecular-weight heparin (LMWH), and aspirin. Although the studies were heterogenous in terms of design, treatment regimen, and proclivity for bias, among the 1228 women studied, anticoagulation did not have a beneficial effect on live birth, regardless of which anticoagulant was evaluated; among women who received aspirin compared with placebo the RR for live birth was 0.94 (95% CI, 0.80-1.11; n = 256), in women who received LMWH compared with aspirin RR was 1.08 (95% CI, 0.93-1.26; n = 239), and in women who received LMWH and aspirin compared with no

treatment RR was 1.01 (95% CI, 0.87-1.16; n = 322).[25]

Given the available data, treatment among those with RPL and inherited thrombophilia is often considered on a case-by-case basis, extrapolating from the treatment of those with APLS, in whom heparin or aspirin is frequently used.[5] Support for antithrombotic treatment in those with inherited thrombophilia and RPL was first published by Brenner and colleagues in a study of 61 pregnancies in 50 women. Enoxaparin was prescribed throughout the pregnancy and 4 to 6 weeks into the postpartum period. About 75% of the pregnancies resulted in a live birth compared with a success rate of 20% in previous pregnancies without anticoagulation. The same investigators later went on to study the efficacy and role of varying doses of enoxaparin.[26] The 2014 TIPPS trial evaluated the use of antepartum dalteparin for the prevention of VTE, pregnancy loss, and placental-mediated pregnancy complication among women with inherited thrombophilia. Women were randomized to receive dalteparin prophylactic dosing or no dalteparin from the day of randomization (< 20 wk gestation) to 37 weeks' gestation. Findings indicate that dalteparin did not reduce the occurrence of VTE, pregnancy loss, or placenta-mediated complications.[27] Among this same population, the EAGeR trial investigated the association between daily aspirin therapy and very early pregnancy losses or euploid losses among women with 1 to 2 prior losses. Women were randomized to daily aspirin and folic acid versus folic acid only in this block-randomized, double-blind, placebo-controlled trial. Medication was continued for ≤6 menstrual cycles, or throughout pregnancy if they conceived, through 36 weeks. Results indicated no association between aspirin therapy and clinically recognized pregnancy losses or implantation failures.[28]

A number of subsequent small studies have been conducted among women with RPL and known inherited thrombophilia, with varying outcome; overall there remains an inability to generalize results. Given the lack of consistent evidence at this time, anticoagulation among women with inherited thrombophilia in an effort to improve pregnancy outcome is not recommended. There is significant data supporting treatment for deep vein thrombosis prevention among this same population, which is discussed in detail elsewhere.

Areas of Ongoing Research

As our knowledge of thrombosis and inflammation expands, it is apparent both related entities are important for successful embryonic implantation and development. Preimplantation factor (PIF) is a 15 amino-acid embryo-derived product integral to maternal adaptation to pregnancy and communication between the mother and embryo.[29] It is secreted by viable gestations detectable at the 2-cell stage in human pregnancies. It not only has utility in diagnostic applications, specifically in predicting successful pregnancy in the bovine model, but also it is a promising therapeutic immunomodulator.[30,31] PIF promotes endometrial receptivity by upregulating α2β-3 integrin expression and promotes embryo decidual adhesion.[29,32] PIF has pleiotropic effects beyond immune modulation including modulation of lymphocyte proliferation, inhibition of natural killer cell activity, and promotion of both neuroprotection and neuroregeneration.[33] PIF's properties and safety profile has allowed it to be fast tracked by the FDA for clinical trial in its first human trial, treating autoimmune hepatitis (ClinicalTrials.gov Identifier: NCT02239562). The field continues to investigate potential diagnostic and treatment modalities aimed at fostering improved pregnancy outcomes for common reproductive and obstetric complications.[34]

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