

Pregnancy and Thrombophilia

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Abstract

Thrombophilic disorders encompass a diverse group of coagulation disorders that potentiate a predisposition for thrombotic events. Amongst the known thrombophilias are antithrombin III deficiency, prothrombin G20210A gene mutation, protein S and protein C deficiency, activated protein C resistance and the antiphospholipid syndrome. Thrombophilia and its influence on pregnancy have been studied for the past 50 years. Both inherited and acquired thrombophilia have been associated with an increased risk of thrombo-embolism as well as an increased risk of pregnancy loss and adverse obstetric outcomes. Some thrombophilias (antiphospholipid syndrome, factor V Leiden mutation and antithrombin III deficiency) confer a higher risk of both venous thrombo-embolism and obstetric complications. There is still no consensus on the optimal management of thromboprophylaxis in future pregnancies. Clearly large well designed and adequately powered multicenter randomised trials are required to clarify the management of thrombophilia in pregnancy especially with a history of adverse obstetric outcome.

Keywords: Pregnancy; Adverse obstetric outcomes; Recurrent miscarriage; Venous thrombosis; Thromboprophylaxis in pregnancy

Introduction

Thrombophilic disorders encompass a diverse group of coagulation disorders that potentiate a predisposition for thrombotic events (e.g. deep vein thrombosis and pulmonary embolism). The term thrombophilia was coined in 1965 following a Norwegian familial study of venous thrombosis [1]. The entity of thrombophilia has also been described as a disorder in which there is abnormally enhanced coagulation [2]. Amongst the known thrombophilias are antithrombin III deficiency, prothrombin G20210A gene mutation, protein S and protein C deficiency, activated protein C resistance and the antiphospholipid syndrome. Thrombophilia and its influence on pregnancy have been studied for the past 50 years. Both inherited and acquired thrombophilia have been associated with an increased risk of thrombo-embolism as well as an increased risk of pregnancy loss and adverse obstetric outcomes. This review aims to provide an overview and update on the influence of the various inherited and acquired thrombophilia in pregnancy.

The Effect of Thrombophilia in Pregnancy

Physiological changes in pregnancy

There are several physiological changes that occur in pregnancy that synergistically create a hypercoagulable state and thus a tendency to clot. Within the haemostatic system there is increased activity of coagulation factors and this is thought to be a protective mechanism to prevent excessive blood loss at childbirth [3]. There is a demonstrable increase in the concentrations of haemostatic components such as von Willebrand factor, factors V, VII, factor X [4] and a dramatic increase is usually observed in factor VIII C. Increases in the levels of fibrinogen factors II, VII, X and XII may also be as high as 20-200%. In contrast, endogenous anticoagulant levels increase minimally. While levels of antithrombin III and protein C remain constant there is a fall in the free and total protein S antigen.

During pregnancy major changes also occur within the fibrinolytic system to meet the haemostatic challenges during pregnancy. An increase in the levels of plasminogen, plasminogen activator antigen, and tissue plasminogen activator is also evident [5]. Simultaneously, the concentration and activity of plasminogen activator-inhibitor (PAI-1)

increases five-fold. Additionally, plasminogen activator-inhibitor (PAI-2) that is not generally detectable in the non-pregnant state is produced by the placenta. These plasminogen activators ensure successive depression of fibrinolytic activity [6].

These dramatic changes within the clotting cascades are further compounded by venous stasis, venous damage, decreased fibrinolysis and decreasing concentrations of some natural anticoagulants promoting the prothrombotic tendency in pregnancy. Thus there is an increased risk of thrombo-embolism and this risk of thrombosis is aggravated in the presence of pathological conditions that cause hypercoagulation, [7] such as thrombophilia.

Prothrombotic, genetic and inflammatory pathophysiology

Several studies have demonstrated an association between the presence of a thrombophilic disorder and adverse obstetric complications such as placental abruption, stillbirth, preeclampsia and recurrent miscarriage [8,9]. The hypothesis is that the pre-existence of a thrombophilic disorder exaggerates the physiologically induced state of hypercoagulation causing microthrombi that disrupt the uteroplacental perfusion [10,11].

However, the mechanisms by which adverse pregnancy outcomes are influenced by the presence of a thrombophilia have not been fully elucidated and are varied and obscure. There is further emerging evidence that the adverse obstetric outcomes may not be solely secondary to a thrombotic state, but that other pathogenetic mechanisms may aggravate the existing hypercoagulable state.

Inflammatory mechanisms [12] and genetic polymorphisms associated with thrombosis may also be implicated [13]. Indeed,

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the complex nature and pathogenesis of thrombophilia-associated pregnancy loss is poorly understood. Despite a significant association between thrombophilia and pregnancy loss [14] placental thrombosis has not been a consistent finding with several cases of pregnancy loss [15,16].

One study has described inhibition of extravillous trophoblastic differentiation in the presence of antiphospholipid antibodies [17]. Other *in vitro* studies have described impaired signal transduction controlling endometrial decidualisation and impaired trophoblastic invasion [13,18,19]. Extensive experiments of antiphospholipid antibodies in mice describe the activation of the complement pathway that generates the potent anaphylatoxin C5a that causes tissue damage by activating inflammatory pathways [20,21].

In vitro observations suggest that the presence of activated coagulation factors results in cell-typespecific changes in trophoblast gene expression [22]. Human placenta is known to express the same factors that control the protein C anticoagulant pathway as that in mice; thrombomodulin (a membrane glycoprotein that activates protein C is localized to the apical membranes of syncytiotrophoblast), a variant of tissue factor protein that was identified in the syncytiotrophoblast cells, and annexin V (an anticoagulant that binds to negative membrane phospholipids) is abundant on normal placentas [23]. Experiments in knockout mice embryos have shown that the fetal genotype itself may exert an important procoagulative effect on placental trophoblasts [24], perhaps in addition to the maternal thrombophilia.

There is further emerging evidence substantiating the “non-prothrombotic” theory. Platelet-leukocyte aggregates (PLA) are cell complexes involved in haemostasis and inflammation. PLA promotes inflammatory and thrombotic activities between platelets and leukocytes. A case control study involving a study group of women with inherited/acquired thrombophilia and age matched controls identified raised PLA levels in the study group compared to the control group [25].

A genetic polymorphism FXIII G-to-T transition (G103T) of the coagulation factor XIII (FXIII) that is responsible for the resistance of thrombus formation, has been described to impair the aggregation of fibrin. This morphological product has been visualised histologically in cases of pregnancy loss [26]. Other polymorphisms of FXIII that have been identified include FXIII A614T (A subunit of FXIII codon 204 of exon 5) and FXIII C1694T (codon 564 of exon 2). Both of these have been found to be associated with pregnancy loss.

Recent literature suggests that both acquired and inherited thrombophilia reflect a general prothrombotic phenotype [27]. A combination of a genetic predisposition and influences in environmental factors may provoke placental vasculature disruption inflicting the various adverse obstetric outcomes that may be observed in pregnancy.

Venous thrombo-embolism in pregnancy with thrombophilia

While there is a heterogeneous pathophysiology associated with adverse obstetric outcome and thrombophilia, the association with the procoagulative adaptations in pregnancy is most likely to be the reason for the increased risk of venous thrombo-embolism in pregnancy. Venous thrombo-embolism in pregnancy and the puerperium remains one of the leading causes of maternal deaths in developed countries [28]. During pregnancy it has been estimated that approximately 22% of all thrombotic episodes occur during the first trimester of pregnancy and 34% and 44% during the second and third trimesters respectively. Approximately one-third of all venous thrombotic events associated with pregnancy occur in the postnatal period [29].

Individuals who have an identifiable thrombophilic defect on laboratory testing as well as a family history of proven venous thrombosis are at greater risk of thrombosis than individuals who have a thrombophilic defect with a negative personal or family history of venous thrombosis [30]. Thrombophilias may be hereditary or acquired or sometimes mixed (as a result of exogenous factors for example with oestrogen use in combined oral contraceptives or hormone replacement therapy) superimposed on a genetic predisposition. Ostensibly, patients who exhibit combinations of thrombophilias are at additional risk of venous thromboembolism [31,32].

The hereditary thrombophilias may be categorised into abnormalities of the natural anticoagulant system or elevated levels of plasma activated coagulation factors. They include Factor V Leiden associated Activated Protein C Resistance (APCR), protein S deficiency, protein C deficiency, prothrombin gene mutation (G20210A), antithrombin III deficiency, and hyperhomocysteinaemia (methylenetetrahydrofolate reductase mutation, C677T MTHFR). The acquired thrombophilias are

antiphospholipidsyndrome, acquired APCR and acquired hyperhomocysteinaemia.

The association between each of these and the risk of thrombosis in pregnancy and an outline of obstetric outcomes is considered below.

Hereditary Thrombophilias

Antithrombin deficiency

Antithrombin is an anticoagulant synthesised in the liver and endothelial cells. It has an inhibitory effect on thrombin, clotting factors X, IX, XI, XII and tissue factor bound VIIa [33]. Antithrombin type I deficiency was the first of the inherited thrombophilias to be described and is the most thrombogenic. It is inherited as an autosomal dominant trait. Antithrombin type I deficiency refers to a quantitative reduction in functionally normal antithrombin while type II antithrombin deficiency describes the production of a qualitatively abnormal protein. Type I deficiency accounts for 80% of symptomatic patients. The Human Gene Mutation Database reported 235 different mutations within the antithrombin gene [34]. More recently, large deletions were identified in some patients exhibiting antithrombin deficiency [35].

The clinical relevance of a distinction between antithrombin type I and antithrombin type II deficiency is important, as there is a higher risk of thrombosis associated with the type I variety. The prevalence of type I mutations in the general population is of the order of 0.02% [36]. The relative risk of venous thromboembolism is around 25 to 50-fold for individuals with type I antithrombin deficiency [37]. During pregnancy the relative risk for venous thrombo-embolism in individuals who have this heritable thrombophilia is as high as 4.1 [37].

Regarding obstetric complications, one study reported a significant increase of miscarriage in association with antithrombin deficiency compared to controls (22.3% versus 11.4% in controls) [38]. Another study demonstrated a fetal loss of between 28 to 32% in women with antithrombin III deficiency compared with 23% in unaffected controls [39]. However no significant association between antithrombin deficiency and recurrent pregnancy loss was found in other studies [40-42]. A Spanish retrospective study found 56% of women with antithrombin deficiency had an adverse pregnancy outcome [43]. Two women suffered a spontaneous miscarriage however no cases of recurrent pregnancy loss were observed.

Prothrombin gene mutation

The prothrombin gene mutation is the second most prevalent genetic abnormality that causes thrombophilia. This mutation occurs as a result of a defect in clotting factor II at position G20210A the G→A transition at nucleotide 20210 in the prothrombin gene. It is inherited as an autosomal dominant trait. The amount of plasma prothrombin is increased by 30% in heterozygous carriers and as much as 70% in homozygosity [44].

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 [45]. This risk may be increased during pregnancy and in the postpartum period. The prothrombin mutation was found to be present in 17% of pregnant women who have suffered a venous thromboembolism [46]. Women with a prior history of venous thrombo-embolism have an increased recurrence risk during pregnancy although recurrence rates range from 0% to 15% among published studies. The risk is likely to be higher in women with a prior unprovoked episode and/or coexisting genetic or acquired risk factors [47].

Several small studies have reported similar frequencies of the prothrombin gene in women with recurrent miscarriage compared to controls, but some documented studies have reported a statistically significant increased frequency. One of these studies report a frequency of 9% in women with recurrent miscarriage while a frequency of 2% occurred in the control group ($p < 0.05$) [48]. A second study reported a frequency of 6.7% compared to 0.8% in the control group ($p < 0.05$) [49]. Another study [50] found a frequency as high as 71% in women with fetal loss while a 30% frequency in controls.

Pooled data from seven other small studies indicate a significant association between the prothrombin gene mutation and recurrent fetal loss [51]. One systematic review reported an odds ratio (OR) of 2.70 (95% CI 1.37-5.34) for recurrent miscarriage in women who were positive for the prothrombin gene mutation compared to those without [43].

The NOHA (Nîmes Obstetricians and Haematologists) [52] first study, a large case-control study nested in a cohort of nearly 32,700 women, of whom 18% had pregnancy loss with their first gestation found on multivariate analysis a clear association between unexplained first pregnancy loss between 10 and 39 weeks gestation and heterozygosity for the prothrombin gene mutation (OR 2.60; 95% CI, 1.86-3.64 [22,52].

A recent prospective cohort study of more than 4000 women found no correlation between the prothrombin gene mutation and recurrent miscarriage [53]. More recently, two European case-control studies concurred with these findings [54,55]. Furthermore, a meta-analysis of prospective cohort studies with a cumulative sample size of 9225 women reported a prevalence of the prothrombin gene mutation of 2.9%. A pooled odds ratio estimate of 1.13 and wide 95% Confidence Interval of 0.64-2.01 for the association of the prothrombin gene mutation and pregnancy loss was reported. The mutation was found to have no association with pre-eclampsia (OR=1.25, 95% CI 0.79-1.99) or for neonates deemed small for gestational age (OR 1.25, 95% CI 0.92-1.70) [56].

Activated protein C resistance

The thrombophilia-activated protein C resistance (APCR) has emerged as the commonest risk factor for venous thrombosis [57-60]. APCR causes prolongation of the activated partial thromboplastin time by interfering with the protein C pathway.

Protein C and its cofactor substrate, protein S, are key components of the anticoagulation pathway. Protein C is a natural anticoagulant and limits the conversion of fibrinogen to fibrin through the degradation of factors Va and VIIIa [58,61] and activated protein C adopts a major role in the coagulation cascade. Activated protein C is only effective when bound to its cofactor protein S. Protein S is available as a cofactor for protein C only when it is bound to C-binding protein. In the basal state, approximately forty percent of protein S is free (unbound) and is available to serve as a cofactor for activated protein C.

Within the clotting cascade, the activated protein C/protein S complex degrades factors Va and factor VIII a, and their loss is associated with a decrease in fibrin formation and hence a reduced ability to form a fibrin clot [36]. Activated protein C normally degrades factors Va and VIIIa by proteolytic cleavage at specific arginine residues. The activation of protein C begins on the surface of endothelial cells through the thrombin-thrombomodulin complex. Activated factor V (factor Va) is a cofactor protein in the prothrombinase complex and together with the serine protease factor Xa, is responsible for conversion of prothrombin to the active enzyme thrombin. Activated protein C regulates the functionality of the complex by proteolytic degradation of factor Va at critical cleavage sites. When factor Va is resistant to degradation by activated protein C the anticoagulation pathway defaults, potentially increasing the risk of thrombosis by several thousand-fold [62,63].

Factor V itself also acts as a cofactor for activated protein C/protein S in the degradation of factor VIIIa. By degrading activated clotting factors Va and VIIIa, activated protein C functions as one of the major inhibitors of the coagulation system. The gene for human factor V has been localised to chromosome 1q21-25 and spans approximately 80 kilobases of DNA consisting of 25 exons and 24 introns and the entire complementary amino acid sequence has been mapped out [64]. The gene is composed of three homologous A-type domains, two smaller homologous C-type domains and a heavily glycosylated B domain that connects the N-terminal A1-A2 region with the light chain and the C-terminal A3-C1-C2 region [65,66]. The majority of alterations are located in the heavily glycosylated B domain. B-domain fragments derived from the activated protein C-mediated cleavage of intact factor V have been directly implicated in the protein C anticoagulant pathway [67,68]. Cleavage of the internal B domain occurs via limited proteolysis by thrombin, the physiological activator of factor V [69].

The earliest description of APCR was derived from a familial study of thrombosis in Leiden in 1993 [68]. This previously unknown thrombophilia was labelled as activated protein C resistance. It was later discovered that activated protein C resistance might manifest as a hereditary or acquired phenomenon.

Congenital/Hereditary APCR

The molecular basis for the hereditary defect was shown to be a point mutation in the factor V gene located on chromosome 1 (1691 G→A) [70-73]. This mutation has been coined the factor V Leiden mutation [74,75]. The factor V Leiden mutation causes the replacement of an amino acid arginine by glycine Arg→Gln at a critical cleavage site 506, the site of the first molecular cleavage of factor Va by APC. This substitution results in diminished APC cleavage of factor Va and continued formation of thrombin by the prothrombinase complex, rendering the activated form of factor V, factor Va, less susceptible to proteolysis by activated protein C. Cleavage of this site by activated protein C is necessary for the exposure of the two additional cleavage sites needed for inactivation. The rate of inactivation is therefore slower than that of normal factor V.

Thus far, the factor V Leiden mutation has been the only genetic defect for which a causal relationship to APCR has been clearly demonstrated. The existence of APCR in the absence of this mutation and the variability of the APCR phenotype in heterozygotes for the R506Q mutation suggested the possibility that alternative gene variations may be responsible for or contribute to APCR. Two other rare, low frequency factor V mutations at other arginine cleavage sites have also been identified: the factor V Hong Kong (Arg 306 Gln) [76] and the factor V Cambridge (Arg 306 Thr) [77]. Although factor V Cambridge may cause activated protein C resistance, no association exists with factor V Hong Kong. These mutations may result in APCR but the clinical association with thrombosis is less clear.

A HR 2 haplotype has been described in association with APCR. The R2 haplotype has been associated with mild APCR (both in the presence and the absence of the factor V Leiden mutation). However not all studies have been convincing regarding the role of the haplotype in clinical disease [78]. The polymorphic sites within the HR2 haplotype do not explain why the haplotype should alter APCR. The two amino acid substitutions coded by the haplotype, 1299His→Arg and 1736 Met→Val also appear to be neutral [79]. Some data suggest that the R2 allele represents a marker in linkage with an unknown defect rather than a functional polymorphism [80].

The Factor V Leiden mutation

The presence of the factor V Leiden mutation produces a protein that is intrinsically resistant to activated protein C, causing the pathological phenotype. The factor V Leiden mutation accounts for a significant percentage of people with a thrombotic event or a family history of thrombosis. A prevalence as high as fifty percent has been quoted in familial studies of venous thromboembolism [57,81]. The expression of the genotype may be heterozygous or homozygous. Zygosity greatly influences the risk of venous thrombosis with a three to ten-fold increased risk of venous thrombosis in heterozygotes and an eighty to hundred-fold increased risk in homozygosity [59]. Some studies have also suggested that different blood group types may confer an additional risk for thrombosis in the presence of the factor V Leiden mutation. Blood types A, B& AB is implicated with an increased risk of thrombosis [82,83].

The prevalence of the mutation does vary in distinct population groups. Among the endogenous populations of Africa and Eastern Asia the incidence of the polymorphism is very low [84]. A frequency of about 3% to 5% in the European Caucasian population has been reported while the highest incidence has been described in Jewish populations (approximately 31.2%) [85,86].

Factor V Leiden and obstetric outcome

With respect to obstetric morbidity parameters and the prevalence of factor V Leiden, findings are polarised with some studies espousing a link while other studies have refuted any association.

The NOHA (Nimes Obstetricians and Haematologists) first study, a large case-control study nested in a cohort of nearly 32,700 women, of whom 18% had pregnancy loss with their first gestation found on multivariate analysis a clear association between unexplained first pregnancy loss between 10 and 39 weeks gestation and heterozygosity for factor V Leiden (OR 3.46; 95% CI, 2.53-4.72) [52].

A significantly higher risk of stillbirth, pre-eclampsia and abruption was described among carriers of the factor V mutation in the EPCOT study [87]. Other studies describe a significant association between the

factor V Leiden mutation and recurrent miscarriage: 15.4% prevalence of the mutation compared to 2.89% in a control group [88] and 25% in another study compared to 7.6% in controls [89].

A recent meta-analysis [56] found that the odds of pregnancy loss in women with the factor V Leiden mutation appears to be 52% higher compared to women without the mutation, however these results are influenced by statistical and clinical heterogeneity in the analysis. Overall the absolute event rate for pregnancy loss was low (4.2%) and only appears slightly higher than the rate of pregnancy loss in women without the factor V Leiden mutation (3.2%) [56].

The validity of testing for the factor V Leiden mutation was explored in a population of women with a history of recurrent miscarriage. Evidence for clinical validity was adequate. The summary odds ratio for association of recurrent pregnancy loss with the factor V Leiden mutation in case-controlled studies was 2.02 (95% confidence interval, 1.60-2.55), with moderate heterogeneity [90].

However, other studies described no increased risk of fetal loss in women with the factor V Leiden mutation compared to those without [10,91,92]. A larger study, [93,94] found a similar prevalence of factor V Leiden in patients with first and second trimester losses compared to a control group of parous women.

A more recent prospective observational study found that heterozygous carriers of the factor V Leiden mutation did not display increased odds of pre-eclampsia, intrauterine death, placental abruption or venous thrombo-embolism. However, almost 50% of the patients within this study were treated with heparin and this could have modulated the results [93,94].

Protein C deficiency

The hereditary pattern of protein C deficiency is generally a pattern of autosomal dominance but exhibits with varying degrees of penetrance. Protein C is a naturally occurring vitamin K dependent protein that is produced in the liver. It is a key component of the protein C system. Upon activation by thrombin, a complex is formed between thrombin, thrombomodulin, protein C and protein S. Protein S functions as an important cofactor in the inhibitory effect of protein C.

Deficiency of protein C primarily causes a loss of function in the protein C gene and the majority of mutations result from single nucleotide substitutions [95]. There are two subdivisions of protein C deficiency i.e. type I (quantitative deficiency) and type II (qualitative deficiency). Type I is observed in the majority of cases [95].

The prevalence of hereditary protein C deficiency in the general population is approximately 0.2 to 0.3% [38] and is detected in 3-5% of patients with venous thrombo-embolism [96]. The risk of venous thrombo-embolism is increased seven to ten fold in patients with this deficiency.

Very few studies have been conducted to look at whether or not there is any association between the protein C deficiency and pregnancy outcome. Two studies that examined the association between protein C deficiency and fetal loss, showed a non-significant association [97,98].

However, a recent study reported an observation of a higher rate of late fetal loss in patients with protein C deficiency compared to non-deficient patients [99].

Protein S deficiency

The majority of protein S deficiency is inherited as a heterozygous

autosomal dominant trait, although the mutation spectrum is rather heterogeneous. There are generally three types of protein S deficiency: type I (decreased protein S activity: decreased total protein S=both bound and free protein S levels and decreased free protein S levels (quantitative defect)), type II (decreased protein S activity: normal free protein S levels and normal total protein S levels (qualitative defect) and type III (decreased protein S activity:decreased free protein S levels and normal total protein S levels (quantitative effect) [100].

Protein S deficiency has a quoted prevalence in the general Caucasian population of between 0 to 0.2% [98]. A higher incidence is quoted amongst Asians 0.48-0.63% [101]. The risk of venous thrombo-embolism associated with protein S deficiency is 1-5% in Caucasians [96] and 12.7% in Asians [101].

With respect to pregnancy complications, a meta-analysis described that protein S deficiency conferred an overall 15-fold increased risk of recurrent pregnancy loss and a 7-fold higher risk of late fetal loss [14].

Methylenetetrahydrofolate reductase deficiency and hyperhomocystinaemia

There are very few studies that have considered this thrombophilia in great detail. Homocysteine is metabolised by either the trans sulfuration pathway (excess homocysteine is converted to methionine) or the remethylation pathway (recycling of homocysteine to form methionine). Increased homocysteine is an independent risk factor for venous thrombo-embolism [102]. The 667 C→T MTHFR mutation results in a thermolabile enzyme with reduced activity for the remethylation of homocysteine. The homozygous form of the mutation induces a state of hyperhomocystinaemia [47]. Hyperhomocystinaemia has a reported prevalence of around 5 % to 16 % in the general population [97,103].

A meta-analysis reported a 3- to 4-fold increased risk of recurrent early pregnancy loss in women with hyperhomocystinaemia [104]. Other studies have also described a high prevalence of hyperhomocystinaemia in women with recurrent pregnancy loss [9,105,106].

Acquired thrombophilia

The most entrenched acquired thrombophilia associated with pregnancy complications is the antiphospholipid syndrome. This thrombophilia is described elsewhere in this book.

Acquired hyperhomocystinaemia

Acquired hyperhomocystinaemia may result from dietary and lifestyle factors such as a reduced intake of folate, vitamin B6 or vitamin B12, excessive caffeine consumption and excessive coffee intake. Certain medical conditions such as hypothyroidism or renal impairment may also cause the acquired form of hyperhomocystinaemia. The Homocysteine Lowering Trial Collaboration [107] 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 of recurrent pregnancy loss concluded that acquired hyperhomocystinaemia is a risk factor [104,106].

Acquired APCR

Although ninety-five percent of cases of activated protein C resistance are due to the factor V Leiden mutation [70], *in vitro* resistance to activated protein C may occur in the absence of the factor V Leiden

mutation. This phenomenon is the entity of acquired activated protein C resistance (APCR) and may be induced by several factors. The various physiological alterations of the clotting factors during pregnancy may potentiate the development of acquired APCR. Other hormone-related milieus, which may encourage acquired APCR, include exogenous oestrogen usage as in the combined oral contraceptive pill and in hormone replacement therapy [108-110].

Acquired APCR may also be demonstrated in protein S deficiency [69], increased antithrombin levels [111] and with increased levels of factor VIIIc [112]. A modified resistance to activated protein C has also been demonstrated in the presence of lupus anticoagulants and anticardiolipin antibodies [113-115]. However, despite the numerous confounding factors that may potentiate APCR, several studies have been able to demonstrate APCR as an independent factor for thrombosis [116,117].

As there is a physiologically induced increased level of APCR in pregnancy, the mechanism of adverse obstetric outcomes and pregnancy loss associated with activated protein C resistance may be due to an exaggeration of the insult in the presence of pre-existing APCR. As with hereditary APCR, there are discrepant results from studies examining the association between amplified APCR and pregnancy loss.

One study expounded that non-factor V Leiden APCR is one of the most common thrombophilic defects associated with recurrent pregnancy loss [89]. They report an incidence of 9% (13/145) in women with fetal losses, but a complete absence of acquired APCR in women in their control group. Another study reported a significantly higher incidence of acquired APCR in women with recurrent first trimester and second trimester losses 8.8% (80/904) and 8.7% (18/207), compared to a control group of parous women 3.3% (5/150) [93].

Another case control study described a fetal loss rate of 75% in women suffering with recurrent miscarriage and who also demonstrated the presence of acquired activated protein C resistance [118].

Despite extensive research within the field of thrombophilia, the specific cause of many thrombotic episodes remains an enigma. Alternative polymorphisms within the active B domain of the factor V gene, was explored by a genetic study [119] to elucidate the existence of acquired APCR. Fifty-one women with recurrent pregnancy loss and acquired APCR were recruited and their factor V gene was intensely analysed to identify single-nucleotide polymorphisms (SNP's). Samples were compared with controls and results showed there was a significantly increased number of specific SNP's within the acquired APCR cohort. This study also explored the theory of whether some SNP's increase the risk of pregnancy loss in women with acquired APCR [119].

Treatment Options During Pregnancy and the Puerperium

Thrombophilia-associated venous thrombo-embolism

There are two categories that warrant consideration. Firstly, there is the treatment of a pregnant patient with a known thrombophilia who has had previous venous thrombo-embolic disease. Secondly, is the consideration of the option of prophylactic treatment against venous thrombo-embolism in a pregnant patient with a known thrombophilia but without a previous venous thrombo-embolic episode.

In the first group, patients may already be prescribed long-term vitamin K antagonists such as warfarin. This poses a problem as warfarin taken during the first trimester of pregnancy may be

potentially teratogenic and may cause serious embryopathy. Warfarin crosses the placenta and congenital abnormalities may occur in 5% of embryos exposed to warfarin between six to twelve weeks gestation [120,121]. It is therefore advisable to discontinue warfarin in the first trimester by bridging with low molecular weight heparin instead.

Few studies have looked at the optimal management of women who have sustained a previous venous thrombo-embolic episode with a thrombophilic disorder. One prospective study described a higher recurrence risk in all trimesters, so strongly advocates the administration of anticoagulant thromboprophylaxis [122].

Guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG) [123] as well as the American College of Chest Physicians [124] recommend antenatal thromboprophylaxis as well as treatment for six weeks in the postpartum period [22]. Patients with antithrombin III deficiency or antiphospholipid syndrome associated with a venous thrombo-embolic event are deemed as having an even higher risk and the recommendation is that the treatment antenatally should be at a higher dose. Postpartum prophylaxis for six weeks is also recommended [123].

Prevention of venous thrombo-embolism in patients with thrombophilia

As the absolute risk of venous thrombo-embolism is variable between the different thrombophilias, the adoption of a case-based approach is advisable. In general, the optimal management for the prevention of venous thrombo-embolism (VTE) in pregnancy in asymptomatic women with a thrombophilia has not been fully elucidated by high-grade evidence. The RCOG [123] advocates at least seven days of postnatal anticoagulation. However, antenatal thromboprophylaxis may also be required. Other attenuating factors may also increase the risk of venous thrombo-embolism, such as obesity, older maternal age, smoking and a family history of thrombo-embolism.

The commonest cause of VTE is the factor V Leiden mutation, so antenatal and postnatal thromboprophylaxis is recommended. The other two specific thrombophilias that should lead to full anticoagulation is antithrombin III deficiency and the prothrombin gene mutation. A systematic review found that asymptomatic women homozygous for factor V Leiden or the prothrombin variant were both at higher risk of VTE and the absolute risks of pregnancy-related VTE of 9-16% has been reported for homozygous V Leiden [43,124,125]. Therefore both antenatal and puerperal prophylaxis is recommended.

A more recent observational study of 416 women who were carriers of the factor V Leiden mutation or the prothrombin gene mutation also noted a reduction in the VTE events when thromboprophylaxis was employed [126].

Thromboprophylaxis to prevent obstetric complications

Despite conflicting evidence and lack of convincing data supporting the use of antithrombotics to prevent adverse obstetric outcome in women with thrombophilic disorders, the prescription of these is pervasive. What is abundantly clear is that, not only are there differences in studies for or against antithrombotic agents but that even the dosages vary from study to study. This does beg the question as to whether the incongruous findings are largely due to inherent differences in study designs and definitions. Proponents favouring antithrombotic therapies tend to acquire results from small observational studies [127]. Others have simply extrapolated evidence from studies involving antiphospholipid syndrome.

Not all studies use a randomisation technique and therefore present the problem of confounding variables. Some studies have reported on the use of anticoagulants on a composite group of thrombophilia while others are confined to a specific thrombophilia. Indeed the specific strength of association between subgroups of inherited thrombophilia (i.e. Antithrombin III and factor V Leiden) and pregnancy loss is variable.

The treatments that are usually favoured are predominantly, various dosages of low dose aspirin, unfractionated heparin and low molecular weight heparin.

Treatment with low dose aspirin is almost ubiquitous in obstetric patients who manifest a thrombophilia. Aspirin reduces thromboxane A₂ thereby improving prostacyclin production and leads to vasodilatation. Two randomised controlled trials [128,129] found no significant difference in pregnancy outcomes between patients with antiphospholipid syndrome who were treated with aspirin versus a placebo.

A large Cochrane review analyzing thirteen trials involving 849 women revealed that a combined therapy of aspirin and unfractionated heparin reduced pregnancy loss by 54% [130]. A further systematic review incorporating three randomized controlled trials compared unfractionated heparin and aspirin treatment versus aspirin alone. The review reported more favourable outcomes in the unfractionated heparin group [131].

In contrast the hepASA randomised controlled trial compared the efficacy of low dose aspirin versus low molecular weight heparin in women with antiphospholipid syndrome. Live-birth rates of 79% were achieved in both groups and the trial was prematurely stopped as no difference was identified between the two arms [132].

There are few trials that have compared the efficacy of unfractionated heparin versus low molecular weight heparin. A recent pilot randomized trial examined unfractionated heparin rather than low molecular weight heparin in women with placental-mediated complications. The study was underpowered to determine any efficacious advantage of the unfractionated heparin therapy [133]. Another trial compared unfractionated heparin therapy with low molecular weight heparin treatment in women with a thrombophilia and reported a more successful pregnancy outcome in the low molecular weight group. The findings of a more recent trial are outlined below.

It is difficult to draw definitive conclusions from small studies regarding unfractionated heparin, but there are more convincing arguments in favour of low molecular weight heparins. Data gathered from several systematic reviews have recommended the use of low molecular weight heparin rather than unfractionated as the agent of choice for antenatal thromboprophylaxis and anticoagulation [134]. Low molecular weight heparin is as effective, safer and the risk of heparin-induced thrombocytopenia is much lower. Furthermore prolonged exposure to unfractionated heparin in pregnancy may result in osteoporosis and fracture formation [135-137].

An earlier case control study recommended anticoagulant therapy for patients with recurrent pregnancy loss and thrombophilia as forty-six of the 61 pregnancies (75%) resulted in a live birth compared to a success rate of 20% in previous pregnancies without antithrombotic therapy [138]. The 50 women in the study were treated with enoxaparin (Low Molecular Weight Heparin) throughout pregnancy and four to six weeks into the postpartum period. Having ascertained the benefit of enoxaparin, the authors conducted a subsequent randomised

controlled trial: the LIVE-ENOX study to compare 40 mg day versus 80 mg day [139]. The trial demonstrated an increase in live birth rate and a decrease in the incidence of complications in thrombophilic women with no demonstrable effect of the different dosages [139].

Indeed the appropriate dose of heparin therapy that will deliver the maximum benefit with lowest risk of side effects has not been determined. It is noteworthy to consider that pharmacokinetics are altered during pregnancy. Studies of fixed dosages during pregnancy have revealed that the levels of anti-Xa factor fluctuate during the course of pregnancy [140]. Sub-therapeutic levels may be rendered during pregnancy due to the increased drug clearance and altered drug distribution [141].

Another study treated selected patients with heritable thrombophilia and recurrent pregnancy loss with enoxaparin and results exhibited a higher live birth rate, 26/37 (70.2%) compared to 21/48 (43.8%) in untreated patients [142]. More recently a case control study not only elicited an increased risk of stillbirth, abruption and pre-eclampsia in women with thrombophilia, but also concluded that heparin was beneficial as a treatment and prevention [11].

A prospective observational study analyzed women who tested positive for antithrombin deficiency, protein C deficiency or protein S deficiency and were followed through the index pregnancy [33]. Thromboprophylactic treatment included low molecular weight heparin, unfractionated heparin and vitamin K antagonists. Twenty-six women (70%) received treatment and no fetal losses occurred. This compares with a 45% fetal loss rate (5/11) in women with no treatment intervention. When comparing fetal loss rates in women without thromboprophylaxis, the presence was the highest with antithrombin deficiency (63%) followed by protein C deficiency (50%). The authors report that thromboprophylaxis reduced the fetal loss rate in women with such inherited thrombophilia by 15% [33]; however small numbers limits this study. In addition, 81% (21/26) of patients receiving thromboprophylaxis in pregnancy had suffered a previous thromboembolic event.

A study specifically examining antithrombin deficiency assessed the pregnancy outcomes for 9 women [42]. Of 18 pregnancies, 67% (12) received low molecular weight heparin, as antithrombin deficiency had not been diagnosed in the other participants at the time. Miscarriage occurred in 11% (2) of patients, one case of pre-eclampsia was diagnosed and 2 women suffered a stillbirth. Three episodes of venous thromboembolism occurred in women without thromboprophylaxis [42].

A population based prospective cohort study of 2480 women to assess the pregnancy outcome of women with the factor V Leiden mutation with a prior fetal loss showed a substantial 'regression towards the mean,' as those with previous low birth weight consequently increased to a high live birth rate [143]. Those with no treatment intervention had in fact the highest birth rate in the study. Evidence such as this supports the argument that antithrombotic prophylaxis is not required for inheritable thrombophilia. A similar study [144] reviewed pregnancy outcome in 35 women with either the factor V Leiden or prothrombin gene mutation compared to a control group. Every participant had suffered a minimum of three pregnancy losses and no anticoagulation therapy was prescribed. The adjusted odds ratio for live birth with the factor V Leiden or prothrombin gene mutation was 0.48(95% CI=0.23-1.01), P=0.05 and therefore results did not reach a statistical significance.

A more recent observational study of 116 women also found that

low molecular weight heparin prophylaxis reduced the risk of obstetric complications in patients who were carriers of the factor V Leiden mutation or prothrombin gene mutation, who previously manifested obstetric complications [126].

The role of anticoagulation therapy in the treatment of patients with hereditary thrombophilia remains to be accurately assessed. No pharmacological therapy, especially in pregnancy should be allowed prior to robust evidence from comprehensive clinical trials. Low molecular weight heparin administration can be laborious with daily subcutaneous injections, often associated with bruising and skin reactions. Furthermore, there are implications with labour epidural or spinal usage and the risk of spinal haematoma [145]. There may also be risks of wound bleeding or wound haematoma formation [146].

Well- designed trials are the solid basis for evidence-based practice. Historical study design and small participant numbers limits the impact found in published data. Recruitment criteria vary significantly even in randomised controlled trials and so conclusions cannot be assumed to be entirely representative. Patients should be counselled and reassured that there is a good prognosis for subsequent pregnancy however if appropriate, they could potentially be included in high quality research to ascertain a more reliable evidence base for prevention of adverse pregnancy outcomes with thrombophilia.

Opinion from authoritative bodies remains divided. The American College of Chest Physicians [124] recommends both aspirin and heparin for treatment in women with antiphospholipid antibodies and recurrent miscarriage while the European Society of Human Reproduction [147] recommends aspirin with or without heparin.

Recent and ongoing trials

The HABENOX trial [148] examined thromboprophylaxis in women who had thrombophilia and a history of recurrent miscarriage and was set up with three treatment arms. Patients were either randomized to enoxaparin (40 milligram) and placebo, enoxaparin (40 milligram) and aspirin (100 milligrams) or aspirin 100 milligram alone. The primary outcome was live-birth rate and secondary outcomes included pregnancy complications. No significant difference in live birth rate or pregnancy complications was observed between the three groups. However, it is worth noting that the trial ended prematurely because of poor recruitment [148].

Another multicenter randomised controlled trial of patients with recurrent miscarriage and antiphospholipid syndrome compared treatment of unfractionated heparin 5000 unitstwice-daily and low dose aspirin with 40 milligram enoxaparin low molecular weight heparin once daily and low dose aspirin. The live-birth rate was found to be 80% in the low molecular weight group compared to 67% in the unfractionated heparin group [149].

The FRUIT study, a multicenter randomised controlled trial [150], (FRagmin®) in pregnant women with a history of Uteroplacental Insufficiency and Thrombophilia: (FRUIT) ISRCTN87325378), enrolled 139 thrombophilic women with prior adverse pregnancy outcomes (pre-eclampsia or small for gestational age infant with delivery prior to 34 weeks). The women were randomised to receive low molecular weight heparin (Fragmin®) and aspirin 80mg or aspirin 80mg alone. They report on a statistically significant reduction in the primary outcome of pre- eclampsia or small for gestational age infant requiring delivery prior to 34 weeks [150].

There are currently two ongoing randomised trials, which

may proffer more clarity. The TIPPSThrombophilia in Pregnancy Prophylaxis trial is investigating antithrombotic therapy in women with congenital thrombophilia and previous pregnancy loss ([<http://www.ClinicalTrials.gov>; identifier: NCT00967382] and the other trial is the Effectiveness of Dalteparin Therapy as Intervention in Recurrent Pregnancy Loss [<http://www.ClinicalTrials.gov>; identifier: NCT00400387].

Conclusion

The different thrombophilias are fairly common amongst women of reproductive ages. What we do glean from prospective studies and the randomised trials that have thus far been published is the reassurance that the majority of women with a known thrombophilia may not experience any pregnancy complication. Conversely however, in obstetric patients who present with a history of adverse obstetric outcomes such as abruption, pre-eclampsia or recurrent pregnancy loss, it is justifiable to screen for the known thrombophilias. Some thrombophilias (antiphospholipid syndrome, factor V Leiden mutation and antithrombin III deficiency) confer a higher risk of both venous thrombo-embolism and obstetric complications. There is still no consensus on the optimal management of thromboprophylaxis in future pregnancies. Clearly large well designed and adequately powered multicenter randomised trials are required to clarify the management of thrombophilia in pregnancy especially with a history of adverse obstetric outcome.

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