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Inherited and Acquired Thrombophilia in Pregnancy

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1. Introduction

The thrombophilia represent a spectrum of coagulation disorders associated with a predisposition for thrombotic events (deep vein thrombosis (DVT) and pulmonary embolism (PE)) (Kaandorp et al, 2009). Inherited thrombophilia include a single-point mutation on the Factor V gene (factor V Leiden (FVL), prothrombin (PT) G20210A gene mutation, deficiencies in protein C and protein S as well as antithrombin (AT) deficiency. The most entrenched acquired thrombophilia is the antiphospholipid syndrome (APS). APS is a non-inflammatory auto-immune disease characterised by thrombosis or pregnancy complications in the presence of antiphospholipid antibodies (Urbanus et al, 2008). Recognized obstetric complications include fetal loss, recurrent miscarriage, intrauterine growth restriction (IUGR), pre-eclampsia and preterm labour (Lassere and Empson, 2004). The association between the diverse group of thrombophilias and adverse pregnancy outcome has been studied for over 40 years with numerous studies identifying varying coagulation defects. A meta-analysis assessing the impact of thrombophilia and fetal loss described varying outcomes and concluded that positive or negative associations were dependent on the type of thrombophilia (Rey et al, 2003). This chapter will focus on inherited and acquired thrombophilia in pregnancy, except for the antiphospholipid syndrome, which is extensively described in other chapters.

2. Coagulation changes in normal pregnancy

During the course of normal pregnancy dramatic changes occur in the haemostatic system. Coagulation factors increase physiologically in pregnancy and this is thought to be an evolutionary mechanism to prevent excessive blood loss at childbirth (Lindqvist, 1999). Furthermore, venous stasis, venous damage, decreased fibrinolysis and decreasing concentrations of some natural anticoagulants synergistically induce a state of hypercoagulation in pregnancy. However these physiological mechanisms also increase the risk of thrombo-embolism and this risk of thrombosis is aggravated in the presence of pathological conditions that cause hypercoagulation (Stirling et al, 1984). A study of the changes in the concentrations of haemostatic components in normal pregnancy demonstrated an increase in von Willebrand factor, factors V, VII, and factor X (Clark et al, 1998). The greatest increase is usually observed in factor VIIIc, although 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.

The fibrinolytic system too, undergoes major changes to meet the haemostatic challenges during pregnancy. An increase in the levels of plasminogen, plasminogen activator antigen, and tissue plasminogen activator is evident as well (Lockwood, 2002). Simultaneously the concentration and activity of plasminogen activator-inhibitor (PAI-1) increases five-fold and an additional plasminogen activator-inhibitor (PAI-2), not generally detectable in the non-pregnant state, is produced by the plasma. These plasminogen activators ensure successive depression of fibrinolytic activity (Walker et al, 1998).

3. Thrombophilia and pregnancy

The term thrombophilia is an umbrella term for a diverse group of blood clotting disorders of the haemostatic mechanisms. The term was coined in 1965 following a Norwegian familial study of venous thrombosis (Egeberg, 1965). Simmons (1997) described thrombophilia as a disorder in which there is a predisposition to thrombosis due to abnormally, enhanced coagulation and elsewhere they are described as disorders of the coagulation systems that are likely to predispose to thrombosis (Walker et al, 2001).

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. It is now becoming clear that there are many genetic abnormalities that impart an increased risk for thrombophilia, and that the presence of more than one abnormality results in a further increased risk of thrombosis (Bertina R M, 1999; Rosendaal FR, 1999). 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 (Lensen et al, 1996). Some genetic variants have been proven to be independent risk factors for venous thrombo-embolism. Amongst these, are Activated Protein C Resistance (APCR), protein S deficiency, protein C deficiency, prothrombin mutation (G20210A), antithrombin III deficiency, and hyperhomocysteinaemia (methylenetetrahydrofolate reductase mutation, C677T MTHFR). Patients who exhibit combinations of thrombophilias seem to be at additional risk of venous thromboembolism (Zoller et al, 1995; Van Boven et al, 1996)).

3.1 Thrombophilia and pregnancy

A successful pregnancy is dependent on the development of an adequate fetomaternal circulation, relying on adequate placental circulation. In pregnancy the pre-existence of a thrombophilic disorder may exaggerate the physiologically induced state of hypercoagulation and therefore potentiate the thrombotic risk. It has been hypothesised that thrombophilia may be associated with serious obstetric complications such as placental abruption, stillbirth, preeclampsia and recurrent miscarriage as a result of microthrombi in the placental circulation resulting in decreased uteroplacental perfusion (Gharavi et al, 2001; Dizon-Townson et al, 1997; Kupfermanc et al, 1999; Coumans et al, 1999).

However, the mechanisms by which adverse pregnancy outcomes are influenced by the presence of a thrombophilia are varied and obscure. Indeed, the complex nature and pathogenesis of thrombophilia-associated pregnancy loss is poorly understood. Whilst several studies have expounded the prothrombotic theory, placental thrombosis has not

been a universal feature in several cases of pregnancy loss (Mousa et al, 2000;Sikkima et al, 2002). There is further emerging evidence that the adverse obstetric outcome may not be solely secondary to a thrombotic state, but that other pathogenetic mechanisms may aggravate the existing hypercoagulable state. Inhibition of extravillous trophoblast differentiation has been described in the presence of antiphospholipid antibodies (Quenby et al, 2005). Furthermore some invitro studies have described impaired signal transduction controlling endometrial decidualisation and impaired trophoblastic invasion (Sebire et al, 2003;Mak et al, 2003;Di Simone et al, 1999). Genetic polymorphisms and inflammatory mechanisms associated with thrombosis may also be implicated (Sebire et al, 2002).

4. Inherited thrombophilia and pregnancy

Hereditary thrombophilias may be categorised into abnormalities of the natural anticoagulant system or elevated levels of plasma activated coagulation factors.

4.1 Prothrombin gene mutation

The prothrombin gene mutation (PT) is signalled by a defect in clotting factor II at position G20210A. This mutation occurs as a result of the G→A transition at nucleotide 20210 in the prothrombin gene. The reported prevalence in Europe is around 2 %to 6% and the risk of venous thrombosis to heterozygous carriers is three times the normal population (Poort et al, 1996). This risk may be increased during pregnancy and in the postpartum period. The PT mutation was found to be present in 17% of pregnant women who have suffered a VTE (Gerhardt et al, 2000). Women with a prior history of VTE have an increased recurrence risk during pregnancy although recurrence rates range from 0% to 15% among published studies. The risk is likely higher in women with a prior unprovoked episode and/or coexisting genetic or acquired risk factors (Kujovic, 2011).

As far as its association with pregnancy loss is concerned, several small studies reported similar frequencies 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 ($p < 0.05$) (Foka et al, 2000). A second study reported a frequency of 6.7% compared to 0.8% in the control group ($p < 0.05$) (Pihusch et al, 2001). Many et al (2002), 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 (Kujovic, 2004). One systematic review reported an odds ratio (OR) of 2.70 (95% CI 1.37-5.34) for recurrent miscarriage with women who were positive for the prothrombin gene mutation compared with those without (Robertson et al, 2006). The NOHA (Nîmes 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 the prothrombin gene mutation (OR 2.60; 95% CI, 1.86–3.64 (Lissalde-Lavigne et al, 2005; Bates, 2010).

More recently, two European case-control studies found no correlation between the prothrombin gene mutation and recurrent miscarriage (Altintas et al, 2007; Serrano et al, 2010). A recent prospective cohort study of more than 4000 women concurred that there is

no correlation (Silver et al, 2010). 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 for 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)(Rodger et al, 2010).

4.2 Antithrombin deficiency

The antithrombin glycoprotein is synthesized in the liver and is the most important physiological inhibitor of thrombin and of the activated clotting factors of the intrinsic coagulation system. It possesses two important functional regions, namely, a heparin-binding domain and a thrombin-binding domain. Antithrombin deficiency was the first of the inherited thrombophilias to be described and is the most thrombogenic. Antithrombin I deficiency refers to a quantitative reduction in functionally normal antithrombin while type II antithrombin deficiency describes the production of a qualitatively abnormal protein. 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. The prevalence of type I mutations in the general population is of the order of 0.02% (Tait et al, 1993). The relative risk of venous thromboembolism is around 25 to 50 -fold for individuals with type I antithrombin deficiency (Rosendaal et al, 1999). Indeed the relative risk for venous thromboembolism during pregnancy in individuals who have this heritable thrombophilia is as high as 4.1(Rosendaal et al, 1999).

One study reported a significant increase in miscarriage in association with antithrombin deficiency compared to controls (22.3% versus 11.4% in controls)(Miletich, 1987). Another study demonstrated a fetal loss of between 28 to 32% in women with antithrombin III deficiency compared with 23 % in unaffected controls (Sanson et al, 1996). However no significant association between antithrombin deficiency and recurrent loss was found in other studies (Hatzis et al, 1999; Roque et al, 2004; Folkeringa et al, 2007). A Spanish retrospective study found 56% of women with antithrombin deficiency had an adverse pregnancy outcome (Robertson et al, 2006). Two women suffered a spontaneous miscarriage however no cases of recurrent pregnancy loss were observed.

Thus far there is insufficient evidence to comment positively or negatively on the relationship between antithrombin deficiency and pregnancy loss, but as it is the rarest thrombophilia, it is unlikely that it will play a major factor in adverse pregnancy outcome.

4.3 Protein C deficiency

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.

The prevalence of hereditary protein C deficiency in the general population is approximately 0.2 to 0.3 % (Miletich et al, 1987). The risk of venous thromboembolism is increased seven to ten fold in patients with this deficiency. Two studies that examined the association between protein C deficiency and fetal loss, showed a non-significant association (Raziel et al, 2001; Gris et al, 1999).

4.4 Protein S deficiency

Protein S deficiency has a prevalence in the general population of between 0 to 0.2% (Gris et al, 1999). In a meta-analysis, protein S deficiency conferred an overall 15-fold increased risk of recurrent pregnancy loss and a 7-fold higher risk of late fetal loss (Rey et al, 2003).

4.5 Methylenetetrahydrofolate reductase deficiency and hyperhomocystinaemia

Homocysteine is metabolised by either the transsulfuration 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 thromboembolism (Perry, 1999). 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 (Kujovic, 2004).

Hyperhomocystinaemia has a reported prevalence of around 5 % to 16 % in the general population (Kumar et al, 2003; Raziel et al, 2001). A meta-analysis reported a 3- to 4-fold increased risk of recurrent early pregnancy loss in women with hyperhomocystinaemia (Nelen et al, 2000(a)). Other studies have also described a high prevalence of hyperhomocystinaemia in women with recurrent pregnancy loss (Quere et al, 1998; Nelen et al (b), 2000; Coumans et al, 1999).

4.6 Activated protein C resistance

Activated protein C resistance (APCR) is an important thrombophilic disorder. The first description of resistance to the effect of activated protein C, added to plasma from patients with a history of deep-vein thrombosis, was reported by Amer et al (1990). APCR refers to the inability to mount an effective anticoagulant response. As described previously, the clotting cascade is a complex system regulating a balance of procoagulation and anticoagulation. 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 integral 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 (Dahlback, 1995; Koster et al, 1993) and activated protein C adopts a major role in the coagulation cascade.

Activated protein C normally degrades factors Va and VIIIa by proteolytic cleavage at specific arginine residues. 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 thereby is available to serve as a cofactor for activated protein C. In the clotting pathway, the activated protein C/protein S complex degrades factors Va and factor VIIIa, and their loss is associated with a decrease in fibrin formation and hence a reduced ability to form a fibrin clot (Tait et al, 1993). The activated form of factor V enhances the activation of prothrombin by several thousand-fold (Nesheim et al, 1979; Rosing et al, 1980). Blood coagulation Factor V is a large glycoprotein synthesized by the liver hepatocytes (Wilson et al 1984; Mazzorana et al, 1989) and megakaryocytes (Gerwitz et al, 1992). It has a molecular weight of 330-kd and circulates in plasma as an asymmetrical single chain. Factor V is also partially stored in platelets (Tracey et al, 1982). The gene for human factor V has been localised to chromosome 1q21-25 and spans approximately 80 kilobases of DNA and consists of 25 exons and 24 introns.

The complete complementary DNA and derived amino acid sequence of the factor V gene have already been determined (Jenny et al, 1997). Analysis of factor V cDNA has demonstrated that the protein is multidomain and contains two types of internal repeats with the following domain structure: A1-A2-B-C1-C2 (Vehar, 1984; Toole, 1984). The gene is composed of 3 homologous A-type domains, 2 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 (Rosing et al, 1997; Ajzner et al, 1999). Most changes are located in the heavily glycosylated B domain (Pittman et al, 1994). 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 (Lu et al, 1996). Cleavage of the internal B domain occurs via limited proteolysis by thrombin, the physiological activator of factor V (Dahlback, 1980). Although Factor V and factor VIII share homologous A and C domains, the B domain of factor V is not homologous to that in factor VIII. Cleavage of the B domain from factor V results in an inert factor V. This suggests that the B domain is of vital importance in activated protein C cofactor activity, and that mutations in this domain may contribute to an impaired activated protein C response (Kostka, 2000).

Activated factor V (factor Va) is a cofactor protein in the prothrombinase complex that, 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. 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. When factor Va is resistant to degradation by activated protein C the anticoagulation pathway defaults, increasing the risk of thrombosis. It was later discovered that activated protein C resistance may present as a hereditary or acquired phenomenon.

4.6.1 Hereditary APCR

The first description of hereditary APCR was derived from a familial study of thrombosis in Leiden in 1993 (Dahlback et al, 1993). Dahlback and his co-workers recognised that prolongation of the activated partial thromboplastin time (APTT), by activated protein C was reported to be considerably less in a large group of patients with venous thrombosis than in a control group of healthy individuals. They termed this previously unknown thrombophilia activated protein C resistance. Subsequently a hereditary defect for activated protein C resistance was described. The molecular basis for this defect was shown to be a point mutation in the factor V gene located on chromosome 1 (1691 G→A) (Bertina et al, 1994; Greengard et al, 1994; Voorberg et al, 1994; Zoller and Dahlback, 1994). This mutation has been coined the factor V Leiden mutation (Aparicio and Dahlback, 1996; Heeb et al, 1995; Nicolaes et al, 1996).

The mutant factor V gene 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) (Chan et al, 1998) and the factor V Cambridge (Arg 306 Thr) (Hooper et al, 1996). 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 FVL). However not all studies have been convincing regarding the role of the haplotype in clinical disease (Luddington et al, 2000). 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 (Soria et al, 2003). Some data suggest that the R2 allele represent a marker in linkage with an unknown defect rather than a functional polymorphism (Lunghi et al, 1996).

4.6.2 The factor V Leiden mutation

The factor V Leiden mutation has a different prevalence in distinct populations with, a founder effect about 20 000 to 34 000 years ago after the divergence of non-Africans from Africans and after the more recent divergence of Caucasians and Mongolians (Seligsohn, 1997). Thus among the endogenous populations of Africa and Eastern Asia the incidence of the polymorphism is very low (Ozawa et al, 1996; Ridker et al, 1997). Chan et al, 1996 reported a frequency of about 3 % to 5 % in the general Caucasian population. A tabulation of the prevalence of the factor V Leiden mutation in various populations, range from 0 % to 32 % (Finan et al, 2002; Villareal et al, 2002). Other sources reveal a frequency as high as 15 % in whites (Rees et al, 1995). The mutation has a high incidence in Jews of approximately 31.2%. Perhaps the most important clinical determinant of factor V Leiden expression is the genotype (heterozygous or homozygous). This confers an approximately three to ten-fold increased risk of venous thrombosis in heterozygotes and an eighty to hundred -fold increased risk in homozygosity (Rosendaal et al, 1995). The risk of recurrent thrombosis is not yet clear. A small retrospective study found that there was no difference in the probability of recurrent thrombosis in heterozygotes compared with controls, but the risk was higher among homozygotes (Rintelen et al 1996). The thrombotic risk also increases with age, and a few studies suggest that among individuals with the factor V Leiden mutation, those with type O blood may have less risk for thrombosis than individuals with type A, B or AB blood (Gonzales et al, 1999; Robert et al, 2000). Among the population of individuals who have a family history of thrombophilia, approximately fifty percent have the factor V Leiden mutation (Griffin et al, 1993; Svensson et al, 1994). Thus, this particular mutation accounts for a significant percentage of people with a thrombotic event or a family history of thrombosis. Indeed activated protein C resistance has emerged as the commonest risk factor for venous thrombosis (Griffin et al, 1993; Koster et al, 1993; Rosendaal et al, 1995; Svensson and Dahlback, 1994).

4.6.3 Hereditary APCR (factor V Leiden) and pregnancy loss

There are several studies that have elucidated the association between hereditary APCR and pregnancy loss. Grandone et al (1997) reported a 31.2% prevalence of factor V Leiden in women with second trimester fetal losses compared to 4.2 % in matched controls. These findings were further supported by Younis et al (2000) who described a significantly higher incidence of factor V Leiden in women with first trimester and second trimester losses compared to a control group; 16%; 22% and 6% respectively. Reznikoff- Etievant et al (2001) also found a higher incidence of factor V Leiden; 10.38% (27/260) compared to a control group (4.7 % (11/240)).

Fouka et al (2000) described a significant difference in the prevalence of factor V Leiden APCR in their study of women with recurrent miscarriage. Similarly a 15.4% prevalence of the mutation was described by Wramsby et al (2000) in their study group whereas a prevalence of only 2.89 % was present in the control group. Sarig et al (2002) found an incidence of factor V Leiden of 25% (36/145) in women with fetal losses compared to 7.6% (11/145) in controls.

In a case control study limited to first trimester losses only, Balasch et al (1997) could not demonstrate any clear association with hereditary APCR. This finding was echoed by Dizon-Townson et al (1997), who did not find hereditary APCR in any of the participating women with idiopathic recurrent miscarriage. Preston et al (1996), in a retrospective study, could not elicit a link between hereditary APCR and first and second-trimester losses either. In a larger study, Rai et al (2001), 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 composite study of the association between the known thrombophilias and fetal loss demonstrated that fetal loss occurred among 10 of 48 women with thrombophilia (21%), and among 10 of 60 control women (17%). There was a similar risk of fetal loss in women with the factor V Leiden mutation compared to those without (Vossen et al, 2003).

The prevalence of factor V Leiden among women with recurrent miscarriage has revealed discordant results. Some studies have espoused a link between the two, while other studies have refuted any association. There appears to be a degree of polarisation in the findings.

The incongruity of the composite results regarding hereditary APCR, is not surprising, as there is a wide variation in patient numbers, inherent differences in study design, and lack of uniformity regarding pregnancy classification.

With regard to other obstetric morbidity parameters, there appears to be a significant increase in rates of stillbirth, pre-eclampsia and abruption concurring, in this respect, with the EPCOT study which found an increased risk of stillbirth (OddsRatio = 3.6 CI= 1.4 to 9.4) among carriers of the factor V mutation (Preston et al, 1996). The EPCOT study defined miscarriage as a pregnancy loss less than 28 weeks and could not detect an increased risk for fetal loss, however the focus of this study was on heritable thrombophilias, and thus excluded acquired ACPR. The association between stillbirth, abruption, and pre-eclampsia, with acquired activated protein C resistance, needed further exploration to draw a definite conclusion, as the limitation of this study, is the small numbers in these groups.

The NOHA (Nîmes 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) (Lissalde-Lavigne et al, 2005).

A recent meta-analysis (Rodger et al, 2010) found that the odds of pregnancy loss in women with FVL appears to be 52% higher as compared with women without FVL, however these results are influenced by statistical and clinical heterogeneity in the analysis. Overall the absolute event rate for pregnancy loss is low (4.2%) and only appears slightly higher than the rate of pregnancy loss in women without FVL (3.2%) (Rodger et al, 2010).

5. Acquired thrombophilias

The antiphospholipid syndrome, described in great detail elsewhere in this book, is an acquired thrombophilia with a well-established role in the aetiology of adverse pregnancy outcomes.

5.1 Acquired activated protein C resistance

As described above, APCR is the most prevalent risk factor for thrombosis. The presence of the factor V Leiden mutation produces a protein that is intrinsically resistant to activated protein C, causing the pathological phenotype. The factor V Leiden mutation accounts for approximately ninety-five percent of cases of activated protein C resistance (Bertina et al, 1994). However in vitro resistance to activated protein C (causing APCR) may occur in the absence of the factor V Leiden mutation. The term used to describe this phenomenon is acquired activated protein C resistance (Clark et al, 2001).

The presence of non-factor V Leiden APCR or acquired APCR may be influenced by many variables. It is evident from the complexity of the coagulation cascade that perturbations in the levels of coagulation levels that play a key role in activating protein C, will affect resistance to activating protein C. Acquired APCR may be demonstrated in protein S deficiency (de Ronde & Bertina, 1994), increased antithrombin levels (Freyburger et al, 1997) and with increased levels of factor VIIIc (Koster et al, 1995; Kraaijenhagen et al, 2000). A modification of resistance to APC has also been demonstrated with the use of exogenous oestrogen as in the combined oral contraceptive pill (Henkens et al, 1995; Rosing et al, 1997) and in hormone replacement therapy (Lowe, et al 1999). The various physiological alterations to the clotting factors during pregnancy may also potentiate the development of acquired APCR (Clark et al, 1998). Lupus anticoagulants and anticardiolipin antibodies are also known to exert their influence on APCR (Oosting et al, 1993; Bokarewa et al, 1994; Martinuzzo et al, 1996). Despite the numerous confounding factors that may potentiate APCR, several studies have been able to demonstrate APCR as an independent factor for thrombosis (Kiehl et al, 1999; de Visser et al, 1999).

5.2 Acquired APCR and pregnancy loss

The majority of documented studies do not explore the entity of acquired activated protein C resistance. However, in those studies that do address this, none of them dispute the definite association between acquired APCR and recurrent pregnancy loss. Younis et al (2000) were intrigued with their finding of a higher prevalence of acquired as opposed to hereditary activated protein C resistance in the second trimester. Rai et al (2000), also 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).

Sarig et al (2002) point out that non-factor V Leiden APCR is one of the most common thrombophilic defects associated with recurrent pregnancy loss. 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. The reported prevalence of acquired activated protein C resistance from studies so far, ranges from 9% to 26.8% in women with first, second and third trimester losses. It would be interesting to ascertain the converse relationship with greater emphasis on the type of pregnancy loss in women with acquired APCR. Ostensibly, it appears that the entity of acquired activated protein C resistance in the pregnancy loss setting cannot be ignored and is indeed gaining importance. There is a physiologically induced increased level of APCR in pregnancy. The mechanism of recurrent pregnancy loss associated with activated protein C resistance may be due to an exaggeration of the insult in the presence of pre-existing APCR.

Several studies of pregnancy loss and APCR have revealed discrepant results, with some demonstrating a convincing association whereas others nullifying any link between the two. However, most published studies have focused exclusively on hereditary APCR leaving the entity of acquired APCR inadequately explored. In a historical case-control study relating pregnancy loss and APCR, Brenner et al (1997) described a 50 % first trimester loss rate, 17% second trimester loss rate and a 47 % intrauterine fetal death rate. However, this study only included a select group of patients attending a specialist haemostasis unit and had a limited number of patients, with only 9 of the 39 patients having acquired APCR.

Balasch et al (1997), could not demonstrate a higher incidence of APCR in a study group of 55 women with first trimester pregnancy loss (1.8%, $n=1/55$) compared to a control group of 50 women 2% (1/50). This study was confined to hereditary APCR. Another case control study which lacked pregnancy loss classification, showed that the incidence of factor V Leiden was significantly higher among women with recurrent miscarriage (cases 8.0% ($n=9/113$) versus controls 3.7% ($n=16/437$) (Ridker et al, 1998), again, not examining acquired APCR. A further case-control study (Younis et al, 2000), showed a significantly higher prevalence of both congenital 19% ($n=15/78$) and acquired activated protein C resistance 19% ($n=15/78$), compared to controls 6% (8/139) and 2% (3/139) respectively. Although, this study ventured a pregnancy loss classification, there were only 15 patients with acquired APCR. In another study, van Dunne et al (2005) has supported the theory that APCR is associated with fetal losses. They determined that women with the factor V Leiden mutation had fewer embryo losses than matched controls.

A more convincing association between pregnancy loss and acquired APCR, which included a classification of pregnancy loss, was described in a small case control study of 7 patients (Tal et al, 1998). However, this study deviated from the definition of recurrent miscarriage and included patients with just one first or a single second trimester loss, and consequently, there was only one patient who had recurrent miscarriage and acquired APCR. More recently, a larger case control study found acquired activated protein C resistance to be significantly higher in women with recurrent early miscarriage 8.8% (80/904) as well as late miscarriage 8.7% (18/207) compared with controls 3.3% (5/150) (Rai et al, 2001). Rai et al clearly distinguished between hereditary and acquired activated protein C resistance, and indeed emphasised the importance of the latter in pregnancy loss, but used a more general classification of pregnancy loss. 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 (Dawood et al, 2003).

The thrombophilia activated protein C resistance (APCR) has emerged as the commonest risk factor for venous thrombosis. APCR has also been implicated in increasing the

propensity for placental thrombosis and subsequent recurrent fetal losses. Despite extensive research within the field of thrombophilia, the specific cause of many thrombotic episodes remains an enigma. The hypothesis of alternative polymorphisms on the factor V gene was explored by Dawood et al (2007) 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 particular SNP's in 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 (Dawood et al, 2007).

More recent work from mouse models has suggested a role for maternal carriage of the factor V Leiden mutation in causing fetal losses in the absence of placental thrombosis. It is suggested that the mutation caused fetal losses in mice by a disruption to the materno-fetal interaction controlling the protein C anticoagulant pathway on the surface of the trophoblast, which led to poor placental development (Sood et al, 2007). Furthermore, there is emerging evidence from knockout mice embryos that the fetal genotype exerts an important procoagulative effect on placental trophoblasts (Sood et al, 2007). 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 (Lanir et al, 2003). Inactivation of the gene for protein C and endothelial protein C receptor gene deletion are (Li et al, 2005) also associated with mice embryo death. In vitro observations suggest that the presence of activated coagulation factors results in cell-type specific changes in trophoblast gene expression (Bates et al, 2010).

5.3 Acquired hyperhomocystinaemia

Hyperhomocystinaemia may be acquired secondary to dietary and lifestyle factors such as a reduced intake of folate, vitamin B6 or vitamin B12, excessive caffeine consumption and excessive coffee intake. The acquired form of hyperhomocystinaemia may also result from certain medical conditions such as hypothyroidism or renal impairment. The Homocysteine Lowering Trial Collaboration (Clark et al, 2007) has suggested that endothelial dysfunction, alteration of platelet reactivity and disruption of prostacyclin pathways, may be some of the mechanisms responsible for the reported venous thrombosis risk as well as the theoretical risk of pregnancy loss. A meta-analysis of ten studies concluded that acquired hyperhomocystinaemia is a risk factor for recurrent pregnancy loss (Nelen et al, 2000).

6. Treatment options in thrombophilia

6.1 Prevention of venous thrombo-embolism

The optimal management for the prevention of venous thrombo-embolism in pregnancy in asymptomatic women has not been fully elucidated by high-grade evidence. Influencing factors include the absolute risk of venous thrombo-embolism and other risk factors such as obesity, older maternal age and smoking. Where the risk of venous thrombo-embolism is increased by other attenuating factors, consideration for antepartum thromboprophylaxis is

justified. The risk of thrombosis is considerably higher in the puerperium so prophylaxis is generally recommended (Bates, 2008).

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 the administration of anticoagulant thromboprophylaxis should be seriously considered (Brill-Edwards et al, 2000).

6.2 Prevention of adverse pregnancy outcome

This is an area that is subject to great debate. Although there is a paucity of data supporting the use of antithrombotics to prevent adverse obstetric outcome in women with thrombophilic disorders, the incongruity largely lies in inherent differences in study designs and definitions. While the American College of Chest Physicians recommends both aspirin and heparin for treatment in women with antiphospholipid antibodies and recurrent miscarriage, the European Society of Human Reproduction recommends aspirin with or without heparin and the British Committee for Standards in Haematology has recently recommended against antithrombotic therapy.

One of the first proponents for the use of antithrombotic prophylaxis was a study that treated 61 pregnancies in 50 women with recurrent pregnancy loss and thrombophilia with enoxaparin (Low Molecular Weight Heparin) throughout pregnancy and 4–6 weeks into the postpartum period. Forty-six of the 61 pregnancies (75%) resulted in live birth compared to a success rate of 20% in previous pregnancies without antithrombotic therapy (Brenner et al, 2003). Subsequently a randomised controlled trial was published; the LIVE-ENOX study comparing varying doses of enoxaparin (Brenner et al, 2005). Results of the trial demonstrated an increase in live birth rate and a decrease in the incidence of complications in thrombophilic women. Doses of 40 mg day and 80 mg day led to similar clinical results (Brenner et al, 2005). 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 (Carp et al, 2003).

Proponents in favour of treatment in the form of low dose aspirin and heparin tend to acquire results from small observational studies (Gris et al, 2005). Not all studies use a randomization technique and therefore present the problem of confounding variables. The strength of association between subgroups of inherited thrombophilia (i.e. AT III, FVL) and pregnancy loss does fluctuate. A large dedicated recurrent miscarriage clinic coordinated a prospective study comparing pregnancy outcome in 25 women whose screening blood tests were positive for the heterozygous form of the factor V Leiden mutation with a control group. Participants in the control group also had suffered at least 3 consecutive miscarriages. The live birth rate was lower in women positive for factor V Leiden (38%) compared to the control group (49%). The authors suggested the use of thromboprophylaxis in future pregnancies (Lindqvist et al, 2006). Prospective observational studies analyzed 37 women positive for antithrombin deficiency, protein C deficiency or protein S deficiency and were followed through the index pregnancy. 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 state that thromboprophylaxis reduces the fetal loss rate in women with such inherited thrombophilia by 15% (Folkerlinga et al, 2007); however small numbers limits this study. It is of upmost importance to state that women were identified and recruited with reference to a large family cohort study and not due to previous recurrent miscarriage. In addition, 81% (21/26) of patients receiving thromboprophylaxis in pregnancy had suffered a previous thromboembolic event. A more recent descriptive retrospective study assessed the pregnancy outcomes for 9 women diagnosed with antithrombin deficiency (Sabadell et al, 2010). Out of a total 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. A significant observation was that no cases of recurrent miscarriage transpired (Sabadell et al, 2010).

Well- designed trials are the solid basis for evidence-based practice. The description of a 'before and after' study design, used in publications to assess the evidence for inherited thrombophilia and recurrent miscarriage has been explored. 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 (Lindqvist et al, 1999). Those with no treatment intervention had in fact the highest current birth rate in the study. Evidence such as this supports the argument that antithrombotic prophylaxis is not required for hereditary thrombophilia in the RM setting. 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 subcuticular injections, often associated with bruising and skin reactions. A Danish study (Lund et al, 2010) 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.

The role of anticoagulation therapy in the treatment of recurrent miscarriage patients with hereditary thrombophilia remains to be accurately assessed. Historical study design and small participant numbers limits the impact found in published data. Recruitment criteria varies significantly even in randomised controlled trials and so conclusions cannot be assumed to represent the recurrent miscarriage setting. Limited numbers of studies incorporate women with at least three consecutive miscarriages as their inclusion criteria and therefore results have to be treated with caution. There is a dearth of well-structured placebo controlled trials in the literature. 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.

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 (Kupferminc et al, 2011).

Clearly, large randomized trials are required to clarify the management of thrombophilia in pregnancy especially with a history of either adverse obstetric outcome (abruption, pre-eclampsia) or pregnancy loss. There are currently 2 ongoing randomized trials, which may proffer more guidance. The TIPPS: Thrombophilia 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].

7. References

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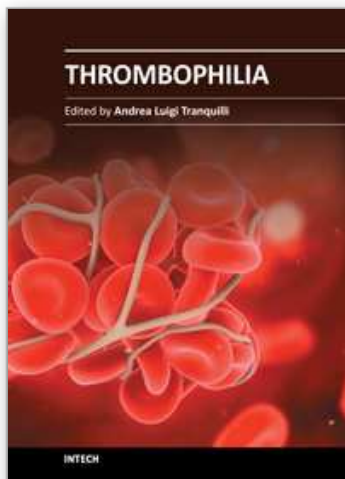
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Thrombophilia(s) is a condition of increased tendency to form blood clots. This condition may be inherited or acquired, and this is why the term is often used in plural. People who have thrombophilia are at greater risk of having thromboembolic complications, such as deep venous thrombosis, pulmonary embolism or cardiovascular complications, like stroke or myocardial infarction, nevertheless those complications are rare and it is possible that those individuals will never encounter clotting problems in their whole life. The enhanced blood coagulability is exacerbated under conditions of prolonged immobility, surgical interventions and most of all during pregnancy and puerperium, and the use of estrogen contraception. This is the reason why many obstetricians-gynecologists became involved in this field aside the hematologists: women are more frequently at risk. The availability of new lab tests for hereditary thrombophilia(s) has opened a new era with reflections on epidemiology, primary healthcare, prevention and prophylaxis, so that thrombophilia is one of the hottest topics in contemporary medicine.

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