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1. Introduction

The thrombophilias 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 thrombophilias 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 VIIIIC, 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 feto-maternal 
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; Kupferminc 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 invivo 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 (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 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-analyses 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 Methylene tetrahydrofolate 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 maternal-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 is localized to the apical membranes of syncytiotrophoblast), a variant of tissue factor protein that was identified in the syncytiotrrophoblast 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 hyperhomocysteinaemia 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 thrombophylaxis 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% (Folkeringa 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

Altintas A, Pasa S, Akdeniz N et al. (2007) Factor V Leiden and G20210A prothrombin mutations in patients with recurrent pregnancy loss: data from the southeast of Turkey Ann Hematol. Oct; 86(10): 727-31.

Ajzner E, Balogh I, Szabo T, Marosi A, Haramura G, Muszbek L. (2002) Severe coagulation factor V deficiency caused by 2 novel frameshift mutations: 2952delT in exon 13 and 5493insG in exon 16 of factor 5 gene. Blood; 99:702-705.

Amer L, Kisiel W, Searles R et al (1990) Impairment of the protein C anticoagulation pathway in a patient with systemic lupus erythematosus anticoagulopathy and thrombosis. *Thromb. Res*; 57:247-258.

Aparicio C and Dahlback B (1996) Molecular mechanisms of activated protein C resistance: properties of factor V isolated from an individual with homozygosity for the Arg506 to Gln mutation in the factor V gene. *Biochemical Journ*; 313:467-472.

Balasch J, Reverter JC, Fabregues F et al (1997) First trimester repeated abortion is not associated with activated protein C resistance. *Hum Reprod* 12:1094-1097.

Bates SM, Consultative Hematology: The Pregnant Patient (2010) *Hematology*: 166-72

Bates SM, Greer IA, Pabinger I et al. (2008) Venous thrombo-embolism, thrombophilia, antithrombotic therapy and pregnancy: American College of Chest Physicians Evidence Based Clinical Practice Guidelines (8th edition). *Chest*; 133:844-86

Bertina RM, Koelaman BP, Koster T et al (1994) Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature*; 369:64-67.

Bertina RM. Molecular risk factors for thrombosis. (1999) *Thromb Haemost*; 82:601-609.

Bokarewa MI, Blomback M, Egberg N, Rosen S. (1994) A new variant of interaction between phospholipid antibodies and the protein C system. *Blood Coagulation and Fibrinolysis*; 5:37-41

Brenner B, Hoffman R, Carp H et al for the LIVE–ENOX Investigators (2005) Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy losses: the LIVE–ENOX study. *J Thromb Haemost*; 3: 227–9.

Brenner B, Mandel H, Lanir N et al (1997) Activated protein C resistance can be associated with recurrent fetal loss. *Brit J Haem* 97:551-554

Brenner B. Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications. (2003) *Thromb Haemost*; 1:2070-2.

Brill-Edwards P, Ginsberg JS, Gent M et al (2000) Safety of withholding heparin in pregnant women with a history of venous thromboembolism. *N Eng J Med*; 343(20): 1439-44.

Carp H, Dolitzky M, Inbal A (2003)Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia. *J Thromb Haemost*; 1: 433–8.
Chan WP, Lee CK, Kwong YL, Lam CK, Liang R. (1998) A novel mutation of Arg 306 of factor V gene in Hong Kong Chinese. *Blood*; 91:1135-1139.

Clark P, Brennand J, Conkie J A, Mc Call F, Greer I A, Walker ID. (1998) Activated protein C rsensitivity, protein C, protein S and coagulation in normal pregnancy. *Thromb Haemost* 79 (6): 1166-1170.

Clark R, Armitage J, Lewington S, Collins R. (2007) B-vitamin treatment trialists’ collaboration of homocysteine-lowering trials for prevention of vascular disease: protocol for a collaborative meta-analysis. *Clin Chem lab Med*; 45 (12): 1575-81.

Coumans AB, Huijgens PC, Jakobs C, Sohorts R, de Visser JJ, van Pampus MG, Dekker GA. (1999) Haemostatic and metabolic abnormalities in women with unexplained recurrent abortion. *Hum Reprod*; 14(1): 211-214.

Dahlback B. (1980) Human coagulation factor V purification and thrombin-catalyzed activation. *J Clin Invest*; 66:583-591.

Dahlback B, Carlsson M, Svensson PJ. (1993) Familial thrombophilia due to a previously unrecognised mechanism characterised by poor anticoagulant response to activated protein C. Prediction of a cofactor to activated protein C. *Proceedings of the National Academy of Sciences of the United States of America*; 90:1004-1008.

Dahlback B. Factor V gene mutation causing inherited resistance to activated protein C as a basis for venous thrombo-embolism. (1995). *J intern Med*; 237:221-227.

Dawood F, Farquharson R, Quenby S, Toh C. H. (2003) Acquired activated protein C resistance maybe a risk factor for recurrent fetal loss. *Fertil Steril*; 80:649-650.

Dawood F, Mountford RG, Farquharson RG, Quenby S. (2007) Genetic polymorphisms on the factor V gene in women with recurrent miscarriage and acquired APCR. *Human Reproduction*; Vol 22 (9): 2546-2453.

de Visser MC, Rosendaal F R & Bertina R M. (1999) A reduced sensitivity for activated protein C in the absence of factor V Leiden increases the risk of venous thrombosis. *Blood*; 93:1271-1276.

Di Simone N, Caliandro D, Castellani R, Ferrazzani S, De Carolis S, Caruso A. (1999) Low-molecular weight heparin restores invitro trophoblast invasiveness and differentiation in presence of immunoglobulin G fractions obtained from patients with antiphospholipid syndrome. *Hum Rep*; 14(2): 489-495.

Dizon-Townson DS, Meline L, Nelson LM, et al. (1997) Fetal carriers of the factor V Leiden mutation are prone to miscarriage and placental infarction. *Am J Obstet Gynecol*; 177:402-405.

Egeber O. Inherited antithrombin deficiency causing thrombophilia. *Thromb Diath Haemorrh* 1965; 13:516-30.

Finan RR, Tamim H, Ameen G, Sharida HE, Rashid M, Almawi WY. (2002) Prevalence of factor V G1691A (Factor V-Leiden) and prothrombin G20210A gene mutations in a recurrent miscarriage population. *Am J Haem*; 71:300-305.

Freyburger G, Javorschi S, Labrouche S and Bernard P. (1997) Proposal for objective evaluation of the performance of various functional APC-resistance tests in genotyped patients. *Thromb Haemost*; 78:1360-1365.

Foka ZJ, Lambropoulos AF, Saravelos H et al. (2000) Factor V Leiden and prothrombin G20210A mutations, but not methyltetrahydrofolate reductase C677T, are associated with recurrent miscarriages. *Hum Reprod*; 15:458-462.
Folkeringa N, Leendert J, Brouwer P et al. Reduction of high fetal loss rate by anticoagulant treatment during pregnancy in antithrombin, protein C or protein S deficient women. 2007 Br J Haematol. 136, 656-661.

Freyburger G, Javorschi S, Labrouche S and Bernard P. (1997) Proposal for objective evaluation of the performance of various functional APC-resistance tests in genotyped patients. Thromb Haemost; 78:1360-1365.

Gerhardt A, Scharf R E, Beckmann M W et al. (2000) Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. N Engl J Med.; 342:374-80.

Gewirtz AM, Shapiro C, Shen YM, Boyd R, Colman RW. (1992) Cellular and molecular regulation of factor V expression in human megakaryocytes. J Cell Physiol; 153:277-287.

Gharavi AE, Pierangeli SS, Levy RA. et al. (2001) Mechanisms of pregnancy loss in antiphospholipid syndrome. Clin Obstet Gynecol.; 44:11-19.

Gonzales Ordonez AJ, Rodriguez JMM, Martin L, Alvarez V Coto E. (1999) The O blood group protects against venous thromboembolism in individuals with the factor V Leiden but not the prothrombin (factor II G20210A) mutation. Blood Coag Fibrin; 10:303-307.

Grandone E, Margaglione M, Colaizzo D et al (1997) Factor V Leiden is associated with repeated and recurrent unexplained fetal losses. Thromb Haemost 77(5):822-824.

Greengard JS, Sun X, Xu X, Fernandez JA, Griffin JH, Evatt B. (1994) Activated protein C resistance caused by Arg506Gln mutation in factor Va. Lancet.; 343:1361-1362.

Gris JC, Quere I, Monpeyroux F et al. (1999) Case control study of the function of thrombophilic disorders in couples with late foetal losses and no thrombotic antecedent- the Nimes Obstetricians & Haematologists Study 5 (NOHA5). Thromb. Haemost; 81; 891-899.

Gris J. C, Mares P. (2005) The long and winding road towards LMWH for pregnancy loss. J Thromb Haemost; 3:224-6.

Griffin JH, Evatt B, Wideman C, Fernandez JA. (1993) Anticoagulant protein C pathway defective in a majority of thrombophilic patients. Blood; 82:1989-1993.

Jenny R, Pittman D, Toole J et al. (1987) Complete Cdna and derived amino acid sequence of human FV. Proc Natl Acad Sci USA; 84:4846-4850

Hatzis T, Cardamakis E, Drivalas E et al. (1999) Increased resistance to activated protein C and factor V Leiden in recurrent abortions:review of other hypercoagulability factors. Eur J Contracept Reprod Health Care; 4:135-144.

Heeb MJ, Kojima Y, Greengard JS, Griffin JH. (1995) Activated protein C resistance: molecular mechanisms based on studies using purified Gln506-factor V. Blood; 85:3405-3411.

Henkens CMA, Bom VJ, Seinen AJ, van der Meer J. (1995) Sensitivity to activated protein C: influence of oral contraceptives and sex. Thromb and Haemost; 73:402-404

Holmes ZR, Regan L, Chilcott I, Cohen H. (1999) The C677T MTHFR gene mutation is not predictive of risk for recurrent fetal loss. Br J Haematol.; 105:98-101.

Hooper WC, Dilley A, Ribiero MJ et al (1996) A racial difference in the prevalence of the Arg506 Gln mutation. Thromb Res; 81:577-581.
Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. (2009) Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome (Review). The Cochrane Library Issue 1.

Kiechl S, Muigg A, Santer P, Mitterer M, Egger G, Oberhollenzer M, Oberhollenzer F, Mayr A, Gasperi A, Poewe W, Willeit J. (1999) Poor response to activated protein C as a prominent risk predictor of advanced atherosclerosis and arterial disease. Circulation; 99:614-619.

Kupferminc MJ, Rimon E, Many A et al. (2011) Low molecular weight heparin treatment during subsequent pregnancies of women with inherited thrombophilia and previous severe pregnancy complications. J Matern Fetal Neonatal Med. 2011 Jan 13. [Epub ahead of print]

Koster T, Rosendaal FR, Briet E, van der Meer FJM, Colly, LP, Treinekens PH, Poort SR, Vandenbroucke JP, Bertina RM. (1993) Venous thrombosis due to a poor anticoagulant response to activated protein C. Leiden Thrombophilia study. Lancet; 342:1503-1506.

Kostka H, Sieger G, Schwarz T, Gehrisch S, Kuhlisch E, Schellong S and Jaross W. (2000) Frequency of polymorphisms in the B-domain of factor V gene in APC-resistant patients. Thromb Res; 99:539-547.

Kraaijenhagen RA, Anker PS, Koopman MMW, Reitsma PH, Prins MHH, van den Ende A, Buller HR. (2000) High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. Thrombosis Haemost; 83:5-9.

Kujovic JL (2011) Prothrombin related thrombophilia. In: Gene Reviews, March 2011

Kujovic JL. (2004) Thrombophilia and pregnancy complications. Am J Obst Gynec.; 191:412-424.

Kumar KS, Govindaiah V, Naushad SE, Devi RR, Jyothy A. (2003) Plasma homocysteine levels correlated to interactions between folate status and methylene tetrahydrofolate reductase gene mutation in women with unexplained recurrent pregnancy loss. J Obstet Gynaecol; 23:55-58.

Kupferminc MJ, Eldor A, Steiman N, Many A, Bar-Am A, Jaffa A. (1999) Increased frequency of genetic thrombophilia in women with complications of pregnancy. NEJM; 340:9-13.

Lassere M, Empson M (2004) Treatment of antiphospholipid syndrome in pregnancy- a systematic review of randomized therapeutic trials. Thromb Res 114:419-26.

Lensen RP, Rosendaal FR, Koster T, Allaart CF, de Ronde H, Vandenbroucke JP, Reitsma PH, Bertina RM. (1996) Apparent different thrombotic tendencies in patients with factor V Leiden and protein C deficiency due to selection of patients. Blood; 88:4205-4208.

Lindqvist P.G, Svensson P. J, Marsaal K et al. (1999) Activated protein C resistance (FV: Q506) and pregnancy. Thromb Haemost; 81:532-7.

Lindqvist P. G, Merlo J. (2006) The natural course of women with recurrent fetal loss. J Thromb Haemost.; 4(4):896-7.

Lissak A, Sharon A, Fruchter O, Kassel A, Sanderovitz J, Abramovica H. (1999) Polymorphism for mutation of cytosine to thymine at location 677 in the methylene reductase gene is associated with recurrent early fetal loss. Am J Obst Gynec; 181:126-130.
Lissalde-Lavigne G, Fabbro-Peray P, Cochery-Nouvellon E, et al. (2005) Factor V Leiden and prothrombin G20210A polymorphisms as risk factors for miscarriage during a first intended pregnancy: the matched case-control ‘NOHA first’ study. *J Thromb Haemost*. 3:2178-2184.

Lockwood CJ (2002) Inherited thrombophilias in pregnant patients: detection and treatment paradigm. *Obstet and Gynecol*; 99:333-341.

Lowe, GDO, Rumley A, Woodward M, Morrison CE, Philippou, H, Lane DA, Tunstall-Pedoe H (1997) Epidemiology of coagulation factors, inhibitors and activation markers: The third Glasgow MONICA survey1. Illustrative reference ranges by age, sex and hormone use. *British Journal Haem*; 97:775-784.

Lu D, Kalfatis M, Mann KG, Long GL. (1996) Comparison of activated protein C/protein S-mediated inactivation of human factor VIII and factor V. *Blood*; 87:4708.

Luddington R, Jackson A, Pannerselvam S, Brwon K, Baglin T. (2000) The factor V R2 allele: risk of venous thromboembolism, factor V levels and resistance to activated protein C. *Thromb Haemost*; 83:204-208.

Lunghi B, Iacovelli L, Gemmat D et al. (1996) Detection of New Polymorphic markers in the factor V gene: association with factor V levels in plasma. *Thrombosis and Haemostasis*; 75 (1): 45-48.

Lund M, Nielsen H. S, Hviid T. V. Hereditary thrombophilia and recurrent pregnancy loss: a retrospective cohort study of pregnancy outcome and complications. *Hum Reprod* 2010. Vol 25 No. 12 pp2978-2984.

Mak IY, Brosens JJ, Christian M et al. (2002) Regulated expression of signal transducer and activator of transcription, Stat 5, and its enhancement of PRL expression in human endometrial stromal cells in vitro. *J Clin Endo Meta*; 87(6): 2581-8.

Many A, Elad R, Yaron Y, Eldor A, Lessing JB, Kupferminc MJ. (2002); Third trimester unexplained intrauterine fetal death is associated with inherited thrombophilia. *Obstet Gynecol*. 99:684-687.

Martinuzzo M, Forastiero, R, Adamczuk Y, Cerrato G, Carreras LO. (1996) Activated protein C resistance in patients with anti-beta2 glycoprotein-I antibodies. *Blood Coag & Fibrin*. 7:702-704.

Mazzorana M, Cornillou B, Baffet G, Hubert N, Eloy R, Guguen-Guilluozo C. (1989) Biosynthesis of factor V by normal adult rat hepatocytes. *Thromb Res*; 54:655-675.

Miletich JP, Sherman L, Broze GL. (1987) Absence of thrombosis in subjects with heterozygous protein C deficiency. *NEJM*; 317:991-996.

Mousa HA, Alfirviewic Z (2000) Do placental lesions reflect thrombophilia state in women with adverse pregnancy outcome? *Hum Reprod*. 8:1830-3.

Nelen WL, Blom HJ, Steegers EA, den Heijer M, Thomas CM, Eskes TK. (2000) Homocysteine and folate levels as risk factors for recurrent early pregnancy loss. *Obstet Gynecol*; 95:519-524.

Nelen WL, Blom HJ, Steegers EA, den Heijer M, Eskes TK. (2000) Hyperhomocysteinaemia and recurrent early pregnancy loss: a meta-analysis. *Fertil Steril*; 74(6): 1196-9.

Nesheim ME, Taswell JB, Mann KG. (1979) The contribution of bovine factor V and factor Va to the activity of prothrombinase. *J Biol Chem*; 254:10952-10962

Nicolaes GAF, Thomassen MCLGD, van Oerle R, Hamulyak K, Hemker HC, Tans G, Rosing J (1996) A prothrombinase-based assay for detection of resistance to activated protein C. *Thromb. Haem*.76: 404-410.
Oosting JD, Derksen RH, Bobbink IW, Hackeng, TM, Bouma, BN, de Groot, PG (1993) Antiphospholipid antibodies directed against a combination of phospholipids with prothrombin, protein C, or protein S: an explanation for their pathogenic mechanism. *Blood*; 81:2618-2625.

Ozawa T, Niiya K, Sakutagawa N. (1996) Absence of factor V Leiden in Japanese (letter). *Thromb Res.*; 81:595-596.

Perry DJ. Hyperhomocysteinaemia. Baillieres Best Practice Res Clin Haematol 1999; 12:451-477.

Pihus R, Buchholz T, Lohse P et al (2001) Thrombophilic gene mutations and recurrent spontaneous abortion: prothrombin mutation increases the risk in the first trimester. *Am J Reprod Immunol*; 46:124-131.

Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. (1996) A common genetic variation in the 3' untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood*; 88:3698-3703.

Preston F E, Rosendaal F R, Walker A I D et al. (1996) Increased fetal loss in women with heritable thrombophilia. *Lancet*; 348: 913-916.

Pittman DD, Tomkinson KN, Kaufman RJ (1994) Post-translational requirements for functional factor V and factor VIII secretion in mammalian cells. *J Biol Chem*; 269:17329.

Quenby S, Mountfield S, Cartwright JE et al (2004) Effects of low-molecular weight and unfractionated heparin on trophoblast function. *Obstet Gynecol*; 104 (2): 354-61.

Quere I, Bellet H, Hoffet M, Janbon C, Mares P, Gris JC. (1998) A woman with five consecutive fetal deaths: case report and retrospective analysis of hyperhomocysteinaemia prevalence in 100 consecutive women with recurrent miscarriages. *Fertil Steril*; 69:152-154.

Rai R, Backos M, Rushworth F, Regan L. (2000) Polycystic ovaries and recurrent miscarriage: a reappraisal. *Hum Reprod*; 15 (3): 612-615.

Rai R, Cohen H, Dave M and Regan L. (1997) Randomised controlled trial of aspirin plus heparin in pregnant women with recurring miscarriage associated with antiphospholipid antibodies. *BMJ*; 314: 253-257.

Rai R, Shlebak A, Cohen H et al (2001) Factor V Leiden and acquired activated protein C resistance among 1000 women with recurrent miscarriage. *Hum Reprod* 16:5 961-965.

Rai R, Backos M, Elgaddal S et al. (2002) Factor V Leiden and recurrent miscarriage: prospective outcome of untreated pregnancies. *Hum Reprod*. Feb; 17(2): 442-5.

Raziel A, Kornberg Y, Friedler S, Schachter M, Sela BA, Ron-El R. (2001) Hypercoagulable thrombophilic defects and hyperhomocysteinaemia in patients with recurrent pregnancy loss. *Am J Reprod Immunol* 45(2): 65-71.

Rees DC, Cox M and Clegg JB. (1995) World distribution of factor V Leiden. *Lancet*;345:1133-1134.

Rey E, Kahn S. R, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta analysis. *Lancet* 2003 361:901-8.

Reznikoff-Etievant MF, Cayol V, Carbonne B, Robert A, Coulet F, Milliez J (2001) Factor V Leiden and G20210 A prothrombin mutations are risk factors for very early recurrent miscarriage. *BJOG* 108:1251-1254.

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Ridker PM, Hennekens CH, Selhub J, Miletich JP, Manilow MR, Stampfer MJ. (1997) Interrelation of hyperhomocystenaemia, factor V Leiden, and risk of future venous thromboembolism. Circulation; 95:1777-1782.

Ridker PM, Miletich JP, Buring JE, Ariyo AA, Price DT (1998) Factor V Leiden mutation as a risk factor for recurrent pregnancy loss. Ann Intern Med 128:1000-1003

Rintelen C, Pabinger I, Knobil P, Lechner K, Mannhalter C. (1996) Probability of recurrence of thrombosis in patients with and without factor V Leiden. Thrombosis and Haemostasis;75:229

Robert A, Aillaud MF, Eschwege V, Randrianjohany A, Scarabin Y, Juhan-Vague I. (2000) ABO blood group and risk of venous thrombosis in heterozygous carriers of factor V Leiden. Thromb Haem; 83:630-631.

Robertson L, Wu Q, Langhorne P et al (2006). The Thrombosis Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Thrombophilia in Pregnancy; a systematic review. Br J Haematol; 132:171-196.

Rodger M A, Betancourt MT, Clark P, Pelle G, Lindqvist H et al. (2010) The Association of Factor V Leiden and Prothrombin Gene Mutation and Placenta-Mediated Pregnancy Complications: A Systematic Review and Meta-analysis of Prospective Cohort Studies. Plos Med; 7 (6): e1000292.

Rosendaal, FR, Koster T, vandenbroucke JP, Reitsma PH. (1995) High risk of thrombosis in patients homozygous for FV Leiden (activated protein C resistance). Blood; 85:1504-1508.

Rosendaal FR. (1999) Risk factors for venous thrombotic disease. Thromb Haemost; 82:610-619.

Rosing J, Tans G, Nicolaes GA, Thomassen MC, van Oerle R, van der Ploeg PM, Heijnen P, Hamulyak K, Hemker HC. (1997) Oral contraceptives and venous thrombosis: different sensitivities to activated protein C in women using second and third generation oral contraceptives. British Journ Haem; 97:233-238

Rosing J, Tans G. (1997) Factor V. Int J Biochem. Cell Biol; 29:1123-1126

Rosing J, Tans G, Govers-Riemslag JWP, Zwaal RFA, Hemker HC. (1980) The role of phospholipids and factor Va in the prothrombinase complex. J Biol Chem; 255:274-283

Roque H, Paidas M, J, Funai E. F et al (2004) Maternal thrombophilias are not associated with early pregnancy loss. Thromb Haemost; 91:290-5.

Sabadielj, Castellas M, Alijotas-Reig J et al. (2010) Inherited antithrombin deficiency and pregnancy: Maternal and fetal outcomes. Eur J Obstet Gynecol Reprod Biol. 149 47-51.

Sanson BJ, Friederich PW, Simioni P, Zanardi S, Hilsman MV, Girolami A et all. The risk of abortion and stillbirth in antithrombin-, protein C-, and protein S-deficient women. Thromb Haemost 1996; 75:387-388.

Sarig G, Younis JS, Hoffman R, Lanir N, Blumenfeld Z, Brenner B (2002) Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage. Fertil Steril 77(2): 342-347

Sebire NJ,Backos M,El Gaddal S et al ( 2003) Placental pathology,antiphospholipid antibodies,and pregnancy outcome in recurrent miscarriage patients. Obstet Gynecol;101(2):258-63

Selighsohn U and Zivelin A (1997) Thrombophilia as a multigenic disorder. Thromb Haemost:78(1):297-301
Serrano F, Lima M. L, Lopes C et al. (2010) Factor V Leiden and prothrombin G20210A in Portuguese women with recurrent miscarriage: is it worthwhile to investigate? Arch Gynecol Obstet

Sikkema JM, Franx A, Bruinse HW, van der Wijk NG, de Valk HW, Nikkels PG. (2002) Placental pathology in early onset pre-eclampsia and intra-uterine growth restriction in women with and without thrombophilia. Placenta. 4:337-42

Silver R. M, Zhao Y, Spong C. Y. et al. (2010) Prothrombin Gene G20210A Mutation and Obstetric Complications. Obstet Gynecol. Vol. 115: 1

Simmons A. (1997) Hematology: a combined theoretical and clinical approach. 2nd ed:Butterworth-Heineman, Massachusetts.

Stirling Y, Woolf L, North WRS. et al. (1984) Haemostasis in normal pregnancy. Thromb Haemost. 52:176-182.

Soria JM, Almasy L, Souto JC, Buil A et al. (2003) Anew locus on chromosome 18 that influences normal variation in activated protein C resistance phenotype and factor VIII activity and its relation to thrombosis susceptibility. Blood. 101(1): 163-167

Svensson PJ and Dahlback B. (1994) Resistance to activated protein C as a basis for venous thrombosis. NEJM; 330:517-522.

Tait RC, Walker ID, Islam SIAM, Mc Call F, Conkie JA, Mitchell R, Davidson JF. (1993) Influences of demographic factors on antithrombin activity in a healthy population. Brit. J. Haem; 84:476-478.

Tal J, Schlamsers LM, Leibovitz Z, Ohel G, Attias D (1999) A possible role for activated protein C resistance in patients with first and second trimester pregnancy failure. Hum Rep 14:1624-1627

Toole JJ, Knopf JL, Wozney JM et al. (1984) Molecular cloning of a cDNA encoding human antithaemophilic factor. Nature; 312:342-347.

Tracy PB, Eide LL, Bowie EJW, Mann KG. (1982) Radioimmunoassay of factor V in human plasma and platelets. Blood; 60:59-63

Urbanus R. T, Derksen R. H, de Groot P. G. (2008) Current insight into diagnostics and pathophysiology of the antiphospholipid syndrome. Blood Rev; 22(2): 93-105.

Van Boven HH, Reitsma PPH, Rosendaal FR, Bayston TA, Chowdury V, Bauer KA, Scharrer I, Conard J (1996) Factor V Leiden (FVR506Q) in families with inherited antithrombin deficiency. Thromb Haemostasis.; 75:417-421.

Vehar GA, Keyt B, Eaton D, Rodriguez H, O’ Brien DP, Rotblat F et al. (1984) Structure of human factor VIII gene. Nature; 321:337-342.

Villareal C, Garcia-Aguirre, Hernandez C, Vega O, Borbolla J R,Collados MT. (2002) Congenital thrombophilias associated to obstetric complications. Journal of Thromb and Thrombolys; 14(2): 163-169.

Voorberg J, Roelse J, Koopman R, Buller H, Berends F, ten Cate JW, Mertens K, van Mourik JA. (1994) Association of idiopathic venous thromboembolism with single point mutation at Arg506 of factor V. Lancet; 343:1535-1536.

Vossen C. Y, Preston F. E, Conard J et al. (2003) Hereditary thrombophilia and fetal loss: a prospective follow-up study. Thromb Haemost, 2:592-596.

Walker I D, Greaves M, Preston F E. (2001) British Society of Haematology Guideline. Brit J Haem; 114:512-528.

Walker I D. (1998) Inherited coagulation disorders and thrombophilia in pregnancy (In) Recent advances in Obstetrics and Gynaecology; 20:Chapter 3:35-64.
Williamson D, Brown K, Luddington R, Baglin C, Baglin I. (1998) FV Cambridge: a new mutation. Wramsby ML, Sten-Linder M, Bremme K. (2000) Primary habitual abortions are associated with high frequency of factor V Leiden mutation. *Fertil Steril* 74(5): 987-991

Wilson DB, Salem HH, Mruk JS, Majerus PW. (1984) Biosynthesis of coagulation factor V by a human hepatocellular carcinoma cell line. *J Clin Invest*; 73:654-661

Younis JS, Brenner B, Ohel G, Tal J, Lanir N, Ben-Ami, M (2000) Activated protein C resistance and Factor V Leiden mutation can be associated with first- as well as second–trimester recurrent pregnancy loss. *Am J Rep Immunology* 43: 31-35

Zoller B and Dahlback B. (1994) Linkage between inherited resistance to activated protein C and factor V gene mutation in venous thrombosis. *Lancet*; 343:1536-1538.

Zoller B, Berntsdotter A, Garcia de Frutos P, Dahlback B. (1995) Resistance to activated protein C is an additional genetic risk factor in hereditary deficiency of protein S. *Blood*; 85:351
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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