Review Article

Thrombophilia in Pregnancy

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Abstract

Introduction**: Thrombophilia refers to disorders which are associated with a persistent hypercoagulable state and a tendency towards thrombosis. They may be inherited, acquired or complex, when genetic factors interact with environmental influences. The objective was to review the various inherited thrombophilias and the antiphospholipid syndrome in relation to pregnancy-related venous thromboembolism and other obstetric complications. **Methods**: A Medline search for articles highlighting thrombophilia and pregnancy-related venous thromboembolism and obstetric complications (pre-eclampsia, recurrent miscarriage, intrauterine growth restriction and placental abruption) was performed. **Results**: The incidence of venous thromboembolism in pregnant Chinese women is similar to that which is reported for Caucasian women. Venous thromboembolism remains a major cause of maternal mortality worldwide as well as locally, where it ranks as the second commonest cause of maternal deaths (rate of maternal deaths from thromboembolism, 0.12 per 10,000 live births and stillbirths). The major risk factors for thrombosis during pregnancy include thrombophilia, operative delivery, advanced maternal age, obesity and pre-eclampsia; these can be identified in about 70% of women who develop the complication during pregnancy and the puerperium. Due to the higher prevalence of factor V Leiden and prothrombin gene G20210A mutation in the Caucasian population, up to 50% of Caucasian women who develop thrombosis during pregnancy or the puerperium test positive for thrombophilia. Recent studies have also shown an association between thrombophilia and adverse obstetric outcomes such as recurrent miscarriage, intrauterine growth restriction, pre-eclampsia and placental abruption. **Conclusion**: Venous thromboembolism is now recognised as a multicausal and multigenic condition. This is particularly evident in pregnancy where multiple risk factors interact and are often identified in women who develop venous thrombosis. With the discovery of factor V Leiden and the prothrombin gene G20210A mutation, inherited thrombophilia can now be detected in a significant proportion of Caucasians who develop venous thromboembolism; however, both these mutations are rarely found in Asians. Identifying women at risk for venous thromboembolism and instituting thromboprophylaxis appropriate to the level of risk remains the key to reducing morbidity and mortality from the condition. Additional research into the intensity, type and duration of thromboprophylaxis for different levels of risk are required. The role of inherited thrombophilia in the pathogenesis of obstetric complications needs to be further defined before screening can be recommended for indications other than venous thromboembolism.

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Introduction

A clear understanding of thrombophilia is becoming increasingly important in the practice of high-risk obstetrics. In addition to their role in thromboembolic disease, there is increasing evidence linking thrombophilia and adverse pregnancy outcomes such as pre-eclampsia, intrauterine growth restriction, placental abruption and recurrent pregnancy loss.

Venous Thromboembolism in Pregnancy

Venous thromboembolism continues to be an important cause of maternal morbidity and mortality worldwide. The incidence of pregnancy-related venous thromboembolism in the Caucasian population is reported to range between 0.7 and 1.3 per 1000 thousand deliveries.[1-3] Chan et al[4] recently reported a similar incidence of 1.88 per 1000 deliveries in pregnant Chinese women. The risk factors identified in their study were also similar i.e., operative delivery, older maternal age, greater body mass index and pre-eclampsia. Heightened awareness of the condition amongst clinicians and availability of easier diagnostic methods partly account for the increased detection of what was once considered an uncommon condition amongst Asians. In quantitative terms, although the majority of thrombotic events occur in the antepartum period, the postpartum period still poses a greater thrombotic risk when one considers this risk in terms of number of events per week (since pregnancy lasts 9 months and the puerperium only 6 weeks).

Local statistics on maternal mortality from the Centre for

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Forensic Medicine over a 10-year period from 1990 to 1999 reveal that pulmonary thromboembolism was the second commonest cause of maternal deaths, accounting for almost a fifth of such deaths.[5] The rate of maternal deaths from thromboembolism (0.21 per 10,000 live births and stillbirths) appears to be comparable to that reported in the Confidential Enquiries into Maternal Deaths in the United Kingdom. Of concern is the fact that in almost half of these deaths, the diagnosis of pulmonary thromboembolism was neither suspected nor provisionally diagnosed, reflecting a failure to appreciate its risk in pregnancy. There is also lack of awareness that the risk of venous thromboembolism exists even in the first trimester of pregnancy. The importance of paying special attention to any woman who develops chest or leg symptoms during pregnancy and the puerperium and carrying out appropriate investigations cannot be overemphasised.

Venous thromboembolism is also associated with significant morbidity such as recurrent thromboembolism, pulmonary hypertension and the post-thrombotic syndrome. The latter is particularly pertinent since venous thrombosis occurs more frequently in the iliofemoral veins than in the calf veins during pregnancy (72% versus 9% respectively), although in the study by Chan et al,[4] more than 80% of the Chinese women had isolated calf vein thrombosis.[6,7]

The 6-fold increased risk of venous thromboembolism during pregnancy is the result of physiological changes in the coagulation and vascular systems. Levels of coagulation factors (factors I, II, VII, VIII, IX and X) are increased together with reduced levels of both total and free protein S and reduced fibrinolysis. This fall in protein S level during pregnancy and the puerperium has also been well documented in Chinese women.[8] Doppler ultrasound studies have demonstrated increase in vessel diameter and fall in flow velocity with increasing gestation.[9] Other important risk factors for venous thromboembolism in pregnant women include increasing maternal age (>35 years), multiparity, obesity (>80 kg), caesarean section particularly emergency sections, pre-eclampsia, prolonged bed rest, previous thromboembolism and thrombophilia. Major risk factors can be identified in about 70% of women who develop venous thrombosis during pregnancy and the puerperium.[2] The current concept of venous thromboembolism as a multicausal and multigenic disease is particularly evident in pregnancy where multiple risk factors, both acquired and genetic, are often identified in women who develop venous thrombosis.

Thrombophilia

The term thrombophilia describes disorders, either inherited or acquired, that are associated with a persistent hypercoagulable state and a tendency towards thrombosis (Table I). There are also complex disorders where genetic and acquired factors interact together. The causes of acquired thrombophilia are varied and include conditions such as the antiphospholipid syndrome, paroxysmal nocturnal haemoglobinuria, myeloproliferative disorders and malignancy. Apart from the antiphospholipid syndrome, the other conditions are rarely encountered in pregnancy and will not be discussed further in this review.

The inherited thrombophilias result from well-defined genetic defects and include antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden and prothrombin gene G20210A mutation. Clinical features which suggest the presence of inherited thrombophilia include positive family history, recurrent episodes of venous thromboembolism, unprovoked disease, unusual sites of thrombosis and young age at presentation (<45 years). Until recently, deficiencies in protein C, protein S or antithrombin were collectively identified in a relatively small percentage (5% to 15%) of patients presenting with venous thromboembolism.[10] Over the past several years, the discovery of factor V Leiden and prothrombin gene G20210A mutation has reaffirmed the important role of genetic risk factors in the pathogenesis of thromboembolic disease (Table II). Due to the high prevalence of these mutations in the Caucasian population, up to 50% of women who developed venous thromboembolism during pregnancy and the puerperium tested positive for thrombophilia.[6]

The prevalence pattern of inherited thrombophilias amongst the Chinese population, however, appears different from that of the Caucasian population. Studies from China and Taiwan report relatively higher prevalence of protein C and protein S deficiency as compared to factor V Leiden and prothrombin gene G20210A mutation in Chinese patients with venous thromboembolism.[11-13] In a study of 60 patients with venous thromboembolism in Singapore, Lim et al[14] detected factor V Leiden in only 3 out of

TABLE I: CLASSIFICATION OF THROMBOPHILIA

Thrombophilia	
Inherited	Antithrombin deficiency
	Protein C deficiency
	Protein S deficiency
	Factor V Leiden
	Prothrombin gene G20210A mutation
Acquired	Antiphospholipid syndrome
	Myeloproliferative disorder
	Malignancy
	Paroxysmal nocturnal haemoglobinuria
	Nephrotic syndrome
Complex	Hyperhomocysteinaemia
	Elevated factor VIII levels
	Elevated factor XI levels

TABLE II: PREVALENCE OF INHERITED THROMBOPHILIAS

Inherited thrombophilia	Healthy population (%)	Unselected patients with VTE (%)
Antithrombin deficiency (type I)	0.02	0.5 – 1.0
Protein C deficiency	0.2 – 0.4	3
Protein S deficiency	0.1	1 – 2
Factor V Leiden	0.05 – 4.8	18.8 – 20
Prothrombin gene G20210A mutation	0.06 – 2.7	5.5 – 6.2

VTE: venous thromboembolism

60 patients (5%); the prevalence of the mutation amongst healthy Malays was also studied and found to be low at 0.5%.

Inherited Thrombophilia

Antithrombin Deficiency

Antithrombin is a major inhibitor of thrombin and also inactivates other serine proteases including factors Xa, IXa and XIa. The mode of inheritance is autosomal dominant. Type 1 deficiency is characterised by reduced levels of immunological and functional antithrombin and type 2 deficiency is characterised by presence of variant antithrombin with functional abnormalities involving either the thrombin inhibiting site or the heparin binding site. Thrombotic risk in antithrombin deficiency is related to the degree of antithrombin activity and the mutation site. Defects at the heparin binding site are associated with relatively lower thrombotic risk compared to those which involve the thrombin inhibiting site.[15] The prevalence of antithrombin deficiency in the general population (0.02%) compared to its prevalence in patients with venous thromboembolism (0.5% to 1.0%) suggests an increased thrombotic risk of at least 50-fold in deficient individuals.[16,17]

Protein C and Protein S Deficiency

Protein C and protein S are vitamin K-dependent inhibitors of coagulation. Protein C becomes activated when thrombin binds to thrombomodulin. Activated protein C (APC), in the presence of free protein S and phospholipids, inactivates factors Va and VIIIa, thereby reducing thrombin generation. Free protein S also possesses anticoagulant effects—it inhibits the prothrombinase complex that converts prothrombin to thrombin and the tenase complex that converts factor X to Xa. The mode of inheritance of protein C and S deficiency is autosomal dominant. Homozygous patients have been rarely described and present with life-threatening thrombotic complications at birth (neonatal purpura fulminans). Prevalence studies suggest that the relative risk of venous thromboembolism for protein C deficiency in non-pregnant patients is about 10.[17] With protein S deficiency, some studies suggest that the risk may be as low as 2-fold but others estimate it to be similar to that of protein C deficiency.[17]

Factor V Leiden

Factor V Leiden is the result of a single point mutation in the gene coding for factor V leading to substitution of arginine by glutamine at position 506.[18] This alters one of the cleavage sites on factor Va, rendering it resistant to degradation by APC. This gives rise to the phenomenon of APC resistance (APCR) where plasma fails to be anticoagulated by the addition of activated protein C *in vitro*. The cofactor activity of factor V Leiden in the inactivation of factor VIIIa by APC is also reduced. Approximately 90% to 95% of APCR is due to factor V Leiden mutation; other causes include genetic polymorphism of the factor V gene (the HR2 haplotype), factor V Cambridge, the presence of lupus anticoagulant or anticardiolipin antibodies, elevated factor VIII levels, pregnancy and the use of combined oral contraceptive pills. The screening test for factor V Leiden mutation is based on measurement of activated partial thromboplastin time (aPTT) in the presence of and in the absence of APC and the results expressed as a ratio (APC sensitivity ratio); resistance is defined when there is insufficient prolongation of aPTT on addition of exogenous APC (a ratio of <2 is abnormal). Diagnosis can be confirmed by polymerase chain reaction test.

There is marked variation in the prevalence of factor V Leiden in different populations.[19] The allele frequency in the general population is about 4% among European whites but it is rare among the native populations of Africa and Asia. The thrombotic risk associated with factor V Leiden is 5- to 10-fold for heterozygotes and 80-fold for homozygotes.[20]

Prothrombin Gene G20210A Mutation

The prothrombin gene G20210A variant was first described by Poort in 1996.[21] The mutation is the result of a G to A substitution at position 20210 of the 3' untranslated region of the prothrombin gene. Heterozygote carriers have 30% higher prothrombin levels compared to healthy controls. The prevalence of this mutation among healthy European controls is about 2% but it is rarely found in non-Caucasians.[22] The prothrombin gene G20210A mutation is associated with 2- to 3-fold increase risk of venous thromboembolism. There is currently no screening test available for the mutation, and diagnosis requires polymerase chain reaction tests.

Acquired Thrombophilia

The Antiphospholipid Syndrome

In addition to its association with arterial and venous thrombosis, the antiphospholipid syndrome is frequently diagnosed in young women following investigation for recurrent miscarriage. Pregnancy loss has been reported to occur at any gestation but fetal loss appears to be more

common and specific for the antiphospholipid syndrome. Oshiro et al[23] found that 50% of pregnancy losses in anticardiolipin antibody or lupus anticoagulant positive women with recurrent miscarriage were fetal deaths (>10 weeks) compared to 15% in antibody negative recurrent miscarries. It is not clear which factors predict whether a woman with antiphospholipid antibodies will have an adverse pregnancy outcome. Some studies suggest that the risk of fetal loss is related to antibody titre as well as antibody isotype particularly the IgG subclass but this is not a constant finding.[24-26] One other important prognostic factor is the previous obstetric history, where prior losses tend to predict future losses. Other well recognised obstetric complications of the antiphospholipid syndrome include early onset pre-eclampsia (<34 weeks' gestation), intrauterine growth restriction and placental abruption.[27] Updated criteria for diagnosis of the antiphospholipid syndrome now include some of these complications (Table III).[28]

The pathogenesis of pregnancy-related complications in the antiphospholipid syndrome is complex. Impaired placental function, probably as a consequence of thrombosis in the uteroplacental circulation, underlies the clinical problems of fetal death, intrauterine growth restriction and pre-eclampsia. Studies have demonstrated spiral artery vasculopathy characterised by absence of normal physiological changes in the myometrial segments of the spiral arteries and arteriolar changes such as lipid laden macrophages in the intima, fibrinoid necrosis in the media and intimal fibroblastic proliferation.[29] Although placental thrombosis and infarction occur frequently in women with the antiphospholipid syndrome, they are neither unique nor universal findings. It is now recognised that antiphospholipid antibodies can affect various aspects of trophoblast differentiation including syncytium formation and invasion, hormone production and annexin V anticoagulant activity.[30] The eventual clinical outcome may then depend on which aspects of trophoblast function are affected by these antibodies.

Despite the successes which have been achieved with heparin and aspirin in women with the antiphospholipid syndrome and recurrent miscarriages, a substantial proportion of such pregnancies are still complicated by problems such as hypertension, fetal growth restriction and pre-term delivery, with persistence of pathological changes in the placenta.[31,32] These findings further emphasise that thrombosis is only part of the pathogenic mechanism and that until the pathogenesis of the antiphospholipid syndrome is completely understood, many aspects of treatment remain empirical.

TABLE III: PRELIMINARY CRITERIA FOR THE CLASSIFICATION OF THE ANTIPHOSPHOLIPID SYNDROME[28]

Clinical criteria

1. Vascular thrombosis: one or more clinical episodes of arterial, venous or small vessel thrombosis in any tissue or organ.
2. Pregnancy morbidity:
   (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation with normal fetal morphology documented by ultrasound or direct examination, or
   (b) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe pre-eclampsia or eclampsia or severe placental insufficiency, or
   (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Anticardiolipin antibody of IgG and/or IgM isotype in blood, present in medium or high titre, on 2 or more consecutive occasions, at least 6 weeks apart, measured by a standard enzyme linked immunosorbent assay for β_2-glycoprotein 1-dependent anticardiolipin antibodies.
2. Lupus anticoagulant present in plasma on 2 or more occasions at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis

Definite antiphospholipid syndrome is considered if at least one of the clinical and one of the laboratory criteria are met.

Other Complex Thrombophilias

Hyperhomocysteinaemia

Hyperhomocysteinaemia may result from a variety of genetic disorders which affect the trans-sulphuration or remethylation pathways of homocysteine metabolism e.g., cystathionine β-synthase deficiency, methylene-tetrahydrofolate reductase (MTHFR) deficiency, thermolabile variant of MTHFR and acquired factors such as chronic renal failure, hypothyroidism, deficiencies of folate, vitamins B_6 and B_{12} and use of drugs such as phenytoin and methotrexate.

Diagnosis is based on either an elevated fasting homocysteine level or performing a methionine loading test. Severe hyperhomocysteinaemia, which results from homozygous deficiency of cystathionine β-synthase or MTHFR, is clearly associated with premature atherosclerosis and venous thrombosis.[33] Case control and cross-sectional studies indicate that mild to moderate hyperhomocysteinaemia is also associated with increased risk of both arterial and venous thrombosis.[34] However, controversy still exists because vascular occlusive disease and elevated homocysteine levels both have multiple causes. Postulated mechanisms, through which hyperhomocysteimaemia contributes to atherogenesis and venous thrombosis, include endothelial cell damage, promotion of platelet activation and aggregation, inhibition of thrombomodulin expression and hence, decreased protein C activation, impaired generation and decreased bioavailability of endothelium-derived relaxing factor/nitric oxide and prostacyclin, and inhibition of tissue

plasminogen activator binding.[34] A number of studies have shown that hyperhomocysteinaemia can be corrected by folic acid alone or in combination with vitamin B_6 or vitamin B_{12}.[35] Although it is clear that vitamins are effective in reducing homocysteine levels, further studies are required to determine if such therapy translates into clinical benefits in terms of reducing the risk of vascular occlusive disease.

Elevated Factor VIII and Factor XI Levels

Elevated levels of factors VIII and XI have been associated with an increased risk of venous thrombosis. Factor VIII levels are partly controlled by genetic factors as well as environmental factors such as pregnancy, use of oestrogens and stress. The risk of venous thrombosis increases with rising factor VIII levels with concentrations above 1500 IU/L being associated with a 6-fold increase in thromboembolic risk.[36] Factor XI is a component of the intrinsic pathway of coagulation and contributes to thrombin generation. Recently, elevated factor XI level was found to be a risk factor for thrombosis with doubling of risk at levels that are present in 10% of the population.[37] Studies have yet to determine whether elevated levels of factor XI are genetically determined. The role of screening for elevated factor VIII and factor XI levels is presently unclear.

Thrombotic Risk in Women with Thrombophilia

The risk of venous thromboembolism in women with thrombophilia depends on the specific thrombophilia, history of previous thromboembolic episodes and additional risk factors. Most of our earlier knowledge on the risk of venous thromboembolism during pregnancy in women with thrombophilia comes from observational studies, which lacked appropriate control groups, and often included women in whom thrombosis had already occurred, as well as women who were identified from symptomatic families. In addition to this selection bias, thrombotic events were not always objectively confirmed. Hence, thromboembolic risk for women with thrombophilia, but who have not yet had a clinical event, is likely to have been overestimated in these earlier studies. Gerhardt et al[38] studied 119 consecutive women with a history of thromboembolism during pregnancy and the puerperium and 233 age-matched normal women. Assuming an incidence of 1 thromboembolic event in 1500 pregnancies, the authors calculated the positive predictive value of each thrombophilia for venous thromboembolism in pregnancy: 1 in 400 for factor V Leiden, 1 in 200 for prothrombin gene G20210A mutation, 1 in 250 for antithrombin deficiency, 1 in 1000 for protein C deficiency and 4.6 in 100 for combination of factor V Leiden and prothrombin gene G20210A mutation. In a retrospective study by McColl et al[2] of 72,000 pregnancies, in which women with venous thromboembolism were tested for thrombophilia and the underlying prevalence of these defects was known for the population, the risk of thrombosis was 1 in 437 for heterozygotes with factor V Leiden, 1 in 2.8 for those with type I antithrombin deficiency, 1 in 42 for those with type II antithrombin deficiency and 1 in 113 for those with protein C deficiency. These data indicate that presence of thrombophilia does not necessarily result in a clinical event and they provide useful clinical information when counselling women with thrombophilia who are contemplating pregnancy with respect to thrombotic risk and thromboprophylaxis.

Thromboprophylaxis

Identifying women at risk for venous thromboembolism and instituting appropriate thromboprophylaxis according to the level of risk remains the key to reducing morbidity and mortality from the condition. Women with previous thromboembolism can be categorised as high or low risk according to the various risk factors shown in Table IV. Additional guidelines for short-term thromboprophylaxis in any woman who undergoes caesarean section have been published by the Royal College of Obstetricians and Gynaecologists.[39]

Brill-Edwards et al[40] studied 125 pregnant women with a single previous episode of venous thromboembolism but without thrombophilia. Only postpartum thromboprophylaxis for a duration of 4 to 6 weeks was given in the subsequent pregnancy. The recurrence rate of antepartum thrombosis was low (2.4%) suggesting that routine antepartum prophylaxis may not be required in these women. In those who have had a previous thromboembolic event plus thrombophilia, there is general consensus that they are at high risk for recurrent thrombosis during pregnancy and should receive prophylaxis with subcutaneous unfractionated heparin or low molecular weight heparin throughout pregnancy and for at least 6 weeks postpartum. Warfarin can be used postnatally and is safe for breastfeeding.

In women identified with thrombophilia, often as a result of family screening, but without a prior clinical event, the answer is less clear. This may partly depend on the specific thrombophilic defect. Because antithrombin deficiency has been associated with a particularly high risk of thrombosis during pregnancy, heparin prophylaxis is recommended throughout pregnancy and the puerperium. With regards to the other inherited thrombophilias, decisions need to be individualised with assessment of other risk factors and discussion with the patient about the potential side effects of heparin such as osteoporosis and heparin-induced thrombocytopaenia if its use is being contemplated throughout pregnancy. Postpartum prophylaxis with heparin or warfarin should be continued for at least 6 weeks. An alternative option is the use of low dose aspirin in the antepartum period, but the efficacy of this needs further study. Aspirin has been shown to prevent deep vein

TABLE IV: THROMBOPROPHYLAXIS IN PREGNANCY ACCORDING TO RISK CATEGORY

Risk category	Risk factor	Thromboprophylaxis
High risk	Previous VTE + thrombophilia Previous VTE + family history Recurrent VTE Antithrombin deficiency ± previous VTE	Antepartum sc UH/LMWH* Postpartum anticoagulation for 6 weeks (sc UH/LMWH or warfarin)
Low risk	One previous episode of VTE and no other risk factors	Antepartum aspirin 75 mg o.d. Postpartum anticoagulation for 6 weeks (sc UH/LMWH or warfarin)
Others	Heterozygous protein C deficiency, protein S deficiency, factor V Leiden or prothrombin gene G20210A mutation without prior VTE or other risk factors	Antepartum aspirin 75 mg o.d. or sc UH/LMWH? Postpartum anticoagulation for 6 weeks (sc UH/LMWH or warfarin)

* Adjusted dose UH/LWMH to maintain activated partial thromboplastin time ratio or anti-Xa activity within therapeutic range for those with antithrombin deficiency or those who are still on anticoagulants; fixed prophylactic dose for the other groups in the high-risk category

LMWH: low molecular weight heparin ; sc: subcutaneous; UH: unfractionated heparin; VTE: venous thromboembolism

thrombosis but its effectiveness is likely to be less than that of heparin or low molecular weight heparin.[41]

Thrombophilia and Adverse Pregnancy Outcomes

Normal development of the uteroplacental vasculature is crucial for successful pregnancy outcome. An underlying thrombophilia may compromise placental perfusion and development by causing thrombosis. Abnormal placental vasculature can result in obstetric complications such as pre-eclampsia, placental abruption, intrauterine growth restriction, miscarriage and stillbirth. There is growing evidence linking adverse obstetric outcomes and inherited thrombophilias. Kupferminc et al[42] performed thrombophilia screening (including factor V Leiden, MTHFR mutation, prothrombin gene G20210A mutation, protein C, protein S, antithrombin, anticardiolipin antibodies and lupus anticoagulant) in 110 women with pregnancies complicated by severe pre-eclampsia, placental abruption, fetal growth restriction or stillbirth and a control group of women with normal pregnancies. The study found that 65% of the women with obstetric complications tested positive for thrombophilia compared to 18% of women with normal pregnancies. However, the results need to be interpreted with caution because, as in previous studies, the authors investigated prevalence of thrombophilias in a selected group of women who had adverse outcomes. The actual risk is not known but it is likely that many women who have inherited thrombophilia will not develop any of these complications. Furthermore, many of the studies involved populations where the prevalence of mutations, such as factor V Leiden and prothrombin G20210A gene, is much higher compared to the prevalence amongst Asians. Prospective longitudinal studies are, therefore, required to determine the risk of obstetric complications in women with thrombophilia.

The potential for these complications to recur in the subsequent pregnancies of women with thrombophilia offers a therapeutic opportunity whereby risk of recurrence can be reduced by treatment with aspirin and heparin. In a recent study, 32 women with adverse obstetric outcomes (pre-eclampsia, placental abruption, fetal growth restriction or stillbirth) and inherited thrombophilia (factor V Leiden, prothrombin gene G20210A mutation, MTHFR mutation, protein C or protein S deficiency) were treated with aspirin and enoxaparin from the 12-week of gestation in a subsequent pregnancy.[43] The rate of obstetric complications was lower than expected from previous studies in similar patient groups. The mean gestational age and birth weight were also significantly higher in the treatment group. It must, however, be emphasised that these data are preliminary and that the study involved a small number of women. Further studies are required; firstly, to quantify the risk of obstetric complications in those with inherited thrombophilia and secondly, to address issues of safety and efficacy of heparin in preventing such adverse outcomes. Until such time, screening for inherited thrombophilia for reasons other than venous thromboembolism cannot be recommended.

Conclusion

Thrombophilia has important implications for the pregnant woman in terms of venous thromboembolism and adverse obstetric outcomes. Venous thromboembolism continues to be an important cause of maternal mortality. Identifying women at risk for venous thromboembolism and instituting appropriate prophylaxis remains the key to reducing morbidity and mortality. In women with a previous episode of venous thromboembolism, the results of thrombophilia screening will have significant impact on thromboprophylactic management during pregnancy and the puerperium. Further research is required to determine the type, intensity and duration of prophylaxis in asymptomatic women with inherited thrombophilia. The role of inherited thrombophilia in the pathogenesis of obstetric complications needs to be further defined before screening can be recommended for indications other than

venous thromboembolism. Only then can appropriate intervention be assessed.

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