Thrombophilia and Adverse Pregnancy Outcome

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Congenital and acquired thrombophilias are the most common predisposing factors for thromboembolism, but they may also contribute to pathophysiological processes involved in recurrent pregnancy loss, fetal death, intrauterine growth restriction, placental abruption, placental infarction, and pre-eclampsia. The most common thrombophilias are deficiencies of antithrombin III, protein C, and protein S, acquired protein C resistance, genetic mutation encoding for factor V Leiden, prothrombin gene, and inherited hyperhomocysteinemia, and antiphospholipid syndrome. Although adverse pregnancy outcomes are more common in women with thrombophilia, the current evidence does not support routine thrombophilia screening of all pregnant women. Selective thrombophilia screening may be justified in certain group of women, particularly those with a history of thromboembolism. More research is required to confirm or refute the causal link between thrombophilia and abnormal placentation, and assess effectiveness and safety of thromboprophylaxis in pregnant women.

Key words: activated protein C resistance; antiphospholipid syndrome; antithrombin III; factor V; hyperhomocysteinemia; pregnancy complications, hematologic; protein C deficiency; protein S deficiency; prothrombin; thrombophilia

Antithrombin III

Antithrombin III deficiency, an autosomal dominant disorder (19), is the most important physiological thrombin inhibitor and inhibitor of factors Xa, IXa, and XIIa. It is the most thrombogenic of all inherited thrombophilias, with a 70-90% life time risk of thromboembolism (3,20).

Two general classes of antithrombin III deficiency have been described. Type I is the most common and is characterized by reduced levels (~50%) of antithrombin. Normal levels but decreased activity of antithrombin III antigen characterize type II (21,22). Type II cases are divided into 3 subtypes, with the same risk of thrombosis apart from IIc, which is an abnormality of the heparin-binding site. The risk of thrombosis is only 6% in heterozygous carriers of IIc (23).

Associated Pregnancy Complications

Preston et al (24) found that women with antithrombin III deficiency had an increased risk of stillbirth (odds ratio 5.2, 95% CI 1.5 to 18.1) and a marginal increase in miscarriage rate (odds ratio 1.7, 95% CI 1.0 to 2.8). By contrast, Gris et al (14) were unable to identify antithrombin III deficiency in 232 women with at least one late stillbirth.
It seems that antithrombin III deficiency is rarely associated with severe preeclampsia, growth restriction, or placental abruption, but this could be a ‘false negative’ finding due to low prevalence of the disease (13,18,25).

**Protein C and Protein S Deficiencies**

Protein C is a naturally occurring anticoagulant, which inactivates factor Va and VIIIa. This process is greatly enhanced in the presence of protein S, another natural anticoagulant, which exists in a free active form (40%) and an inactive form bound to C4b-binding protein (60%) (3).

Protein C deficiency can be found in approximately 1 in 500 healthy individuals (26). It may result from numerous mutations, although two primary phenotypes are known. Type I is characterized by a parallel reduction in protein C antigen and functional activity. Less common type II is associated with functionally abnormal protein C molecules (19,23).

It is likely that the incidence of protein S deficiency is similar to that of protein C deficiency (27). Protein S deficiency presents with one of three phenotypes. Type I is characterized by low levels of both free and total protein S, type II has reduced functional but normal free and total protein S, and type III has low free protein S but normal total protein S (28,29).

**Associated Pregnancy Complications**

Data from the European Prospective Cohort on Thrombophilia study showed a modest increase in the risk of stillbirth among women with protein C deficiency (1.2% vs 0.6%, odds ratio 2.3, 95% CI 0.6 to 8.3) and protein S deficiency (1.9% vs 0.6%, odds ratio 3.3, 95% CI 1.0 to 11.3), but no significant difference in the risk of miscarriage compared with controls (15.8% vs 11.6%, and 14.6% vs 11.6%, respectively) (24).

Sanson et al (30) observed a two-fold increase in fetal loss after 8 weeks’ gestation among women with inherited thrombophilia compared with their unaffected relatives. The risk was greater for protein C and antithrombin III deficiency than for protein S deficiency. By contrast, Gris et al (14) found increased prevalence of protein S deficiency (odds ratio 22, 95% CI 2.8 to 170) and activated protein C resistance (odds ratio 4.8, 95% CI 1.8 to 12.4) in women with at least one late fetal loss compared with matched controls. However, there was no difference between the two groups in the prevalence of deficiencies of protein C and antithrombin III, prothrombin gene mutation (G20210A), or homozygous C677T mutation of the methylene-tetrahydrofolate reductase gene (14).

Overall, it seems that protein S deficiency may be more important than protein C deficiency as a risk for severe pregnancy complications. Dekker et al (25) reported a 25% prevalence of protein S deficiency in women with severe early onset pre-eclampsia, compared with only 1% prevalence of protein C deficiency. Their observation is consistent with others (4,13,18).

**Activated Protein C Resistance**

Activated protein C resistance was described in 1993 (31). More than 90% of cases are due to factor V Leiden mutation (32,33), a guanine to adenine substitution in nucleotide 1691 that results in substitution of a glutamine for arginin at position 506 in factor V polypeptide (FVQ506). The mutant factor V molecules are resistant to proteolytic inactivation by activated protein C and retain procoagulant activity. Factor V Leiden mutation is inherited as an autosomal dominant trait (34,35). It is present in 5-9% of European population but is rare in Asians and Africans (36,37). It is found in a substantial proportion of pregnant and non-pregnant women with thrombotic events (Table 2).

**Associated Pregnancy Complications**

It is unclear whether there is an increased risk of fetal loss in pregnant women with factor V Leiden mutation. The European Prospective Cohort on Thrombophilia study compared the risk for fetal loss in a cohort of 571 women with inherited thrombophilia (deficiencies of antithrombin III, protein S, and C, and activated protein C resistance) with 395 controls (24). Overall, the total fetal loss and stillbirths were more likely in women with any thrombophilia (odds ratio 1.4, 95% CI 1.2 to 1.7) compared with controls.

**Table 1. Placental vascular complications associated with thrombophilia (adapted from 15)**

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Pregnancy complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>miscarriage</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>++</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>+</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>+</td>
</tr>
<tr>
<td>Dysfibrinogenaemia</td>
<td>+</td>
</tr>
<tr>
<td>APC resistance</td>
<td>++</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>++</td>
</tr>
<tr>
<td>MTHFR C677T</td>
<td>+</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>+</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>+</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>++</td>
</tr>
<tr>
<td>Combined defect</td>
<td>++</td>
</tr>
</tbody>
</table>

1.01 to 1.82 and 3.6, 95% CI 1.4 to 9.4, respectively).

Subgroup analysis revealed a modest increase of still-birth but not of miscarriage in women with factor V Leiden mutation (odds ratio 2, 95%CI 0.5 to 7.7 and 0.9, 95% CI 0.5 to 1.5, respectively) (24).

Rai et al (39) found a significant increase in the prevalence of activated protein C resistance in women with recurrent miscarriage with at least one second-trimester loss, compared with women with first trimester recurrent miscarriage or parous controls. This link to fetal loss during the second trimester is further supported by Grandone et al case-control study (40). However, other investigators dispute the correlation between recurrent miscarriage and factor V Leiden mutation (41,42) (Table 3). These data from case-control and cohort studies suggest that recurrent first-trimester miscarriage is not associated with the factor V Leiden mutation, although second-trimester miscarriage may be. It is possible that first-trimester miscarriages reflect failure in implantation, whereas second-trimester miscarriages may be caused by thrombotic event in the placenta (47).

Although the number of studies is still limited, there is increasing evidence of association between activated protein C resistance and hypertensive disorders. In an uncontrolled study of women with a history of severe early-onset preeclampsia, Dekker et al (25) found that 16% of women had activated protein C resistance, which was higher than expected in their population. Nagy et al (48) reported increased prevalence of factor V Leiden mutation among Hungarian women with severe preeclampsia (18.8%), as compared with healthy pregnant controls (7%) (odds ratio 3.06, 95% CI 1.03 to 9.13). Their results are consistent with others (6,49).

The association of factor V Leiden mutation and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) has also been evaluated (50,51). One third of women with a prior history of HELLP syndrome had evidence of activated protein C resistance, but factor V Leiden mutations were only identified in 19% of them (50).

There is a growing evidence to suggest an association between factor V Leiden mutation and/or activated protein C resistance and placental abruption. Two recent reports have found prevalence rates of factor V Leiden mutation in women with placental abruption as high as 25% and 30% (18,52).

The association between factor V Leiden mutation and fetal growth restriction is less clear. De Vries et al (13) identified factor V Leiden mutation in only one out eight normotensive women with fetal growth restriction. In contrast, Kupferminc et al (18) colleagues reported a 1.9-fold increased prevalence of factor V Leiden mutation among women with fetal growth restriction, compared with healthy controls (95% CI 0.6 to 6.3).

The consequences of factor V Leiden mutation in the fetus have also been evaluated (42). Of particular concern is a report of three infants with cerebral palsy due to cerebrovascular accidents who were heterozygous for factor V Leiden mutation (53).

## Acquired Activated Protein C Resistance

Acquired activated protein C resistance, not due to factor V Leiden mutation, has recently been identified as an independent risk factor for venous thrombosis (54). In Italy, a cross-sectional population-based study of 15,109 white participants (8,017 women and 7,092 men) between

### Table 2. Frequency (%) of inherited thrombophilia in the general population and in patients with venous thrombosis (adapted from 38)

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Frequency of inherited thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>general population</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>5</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>2</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>0.2</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>?</td>
</tr>
<tr>
<td>Hyperhomocysteinemia (&gt;18.5 mmol/L)</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 3. Factor V Leiden, activated protein C resistance (APCR), and miscarriage

<table>
<thead>
<tr>
<th>Study (ref.)</th>
<th>Study population</th>
<th>Prevalence of factor V Leiden, APCR, or both</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>patients</td>
</tr>
<tr>
<td>Rai et al (39)</td>
<td>Women with miscarriage: a. confined to first-trimester</td>
<td>4/70 (5.7)</td>
</tr>
<tr>
<td></td>
<td>b. including at least one second-trimester</td>
<td>10/50 (20)</td>
</tr>
<tr>
<td>Grandone et al (40)</td>
<td>Women with ≥2 miscarriages</td>
<td>7/43 (16)</td>
</tr>
<tr>
<td>Balasch et al (41)</td>
<td>Women with ≥2 first-trimester miscarriages</td>
<td>1/55 (2)</td>
</tr>
<tr>
<td>Dizon-Townson et al (42)</td>
<td>Women with ≥3 miscarriages</td>
<td>0/40</td>
</tr>
<tr>
<td>Dizon-Townson et al (43)</td>
<td>Women with ≥3 miscarriages</td>
<td>12/139 (8.6)</td>
</tr>
<tr>
<td>Kidker et al (44)</td>
<td>Women with recurrent abortion</td>
<td>9/113 (8)</td>
</tr>
<tr>
<td>Brenner et al (45)</td>
<td>Women with ≥3 in first-trimester, 2 in second-trimester, or 1 in third-trimester</td>
<td>24/76 (32)</td>
</tr>
<tr>
<td>Foka et al (46)</td>
<td>Women with recurrent miscarriages</td>
<td>15/80 (19)</td>
</tr>
</tbody>
</table>

*Not significant.
18 and 65 years of age, found activated protein C resistance in 30 participants with documented venous thromboembolism (55). However, only 10 participants (33.3%) were carriers for the factor V Leiden mutation and 20 (66.6%) had no factor V Leiden mutation or any other known mutation (55). There is strong evidence suggesting that the changes in the plasma response to activated protein C, defined as activated protein C sensitivity ratio, is associated with changes in the hemostatic system (56).

Tai et al (57) found increased prevalence of acquired activated protein C resistance in women with first or second trimester pregnancy loss (5.6%), when compared with healthy controls (2.4%).

Although the number of studies remain limited, there is evidence of an association between acquired activated protein C resistance and hypertension during pregnancy, Van Pampus et al (9) reported an increased prevalence of activated protein C resistance in 284 women with a history of severe preeclampsia, compared with controls (11.3% vs 1.5%). Factor V Leiden mutation was identified in only 6% of these patients (9). The prevalence of activated protein C resistance was almost twice as high in those who delivered before 28 weeks of gestation (18%), as compared with those who delivered later (9.8%) (9). These findings are in agreement with those of Minuro et al (58), who found an increased prevalence of activated protein C resistance (22%) in 50 pregnant women with severe preeclampsia compared with matched controls (2.7%). Only 4 patients (8%) were carriers of the factor V Leiden mutation (58).

The correlation between acquired activated protein C resistance, thrombin-antithrombin complex (a marker of thrombin generation), and birth weight has also been investigated. In a prospective longitudinal study of 128 low-risk pregnant parous Scottish women, Clark and colleagues reported an inverse correlation between activated protein C ratio (examined at 28-32 weeks’ gestation) and anti-thrombin complex concentration (59). Furthermore, the mean birth weight centile among babies of women with increased activated protein C resistance was significantly lower than of those with no increase in resistance (46 vs 61, respectively) (59).

**Hyperhomocysteinemia**

Homocysteine is derived from dietary methionine and is present in plasma in low concentrations of 5-15 mol/L. Hyperhomocysteinemia can result from abnormalities of any of the enzymes involved in the methionine pathway (Fig. 1). The condition can be diagnosed by measuring homocysteine levels using gas-chromatography-mass spectrometry or other sensitive biochemical methods. Methionine loading can improve sensitivity (27). The disorder is classified into three categories according to the serum fasting level of homocysteine: severe (>100 mol/L), moderate (25-100 mol/L), or mild (16-24 mol/L) (3). Plasma homocysteine levels are strongly influenced by plasma folate, vitamin B12, and vitamin B6 levels. Deficiency of these nutritional factors is major cause of mild to moderate hyperhomocysteinemia (19,60).

Severe hyperhomocysteinemia results from autosomal recessive homocysteine deficiency in either cystathionine B-synthase or methylene-tetrahydrofolate reductase. Both conditions are associated with neurological abnormalities, premature atherosclerosis, and recurrent thromboembolism (61).

*Mild and moderate* hyperhomocysteinemia may be due to either autosomal dominant (heterozygous) deficiencies in cystathionine B-synthase (0.3–1.4% of population) or from homozygosity for C677T methylene-tetrahydrofolate reductase thermo-labile mutation, which is present in 11% of white Europeans (62). The high prevalence highlights the importance of universal pre-conception folate supplementation (61). Obviously, people with mild and moderate hyperhomocysteinemia are at an increased risk of atherosclerosis, cardiovascular disease (63,69), and arterial and venous thrombosis (3,65). Women of childbearing age are at risk of having a child with neural tube defect or suffering recurrent miscarriage (3).

Nelen et al (66) found that women who have experienced two or more consecutive pregnancy losses before 17 weeks’ gestation are two to three times more likely to be homozygous for the thermo-labile variant of methylene-tetrahydrofolate reductase, compared with matched controls with successful pregnancy outcome. However, other investigators reported that homozygosity for the methylene-tetrahydrofolate reductase C677T mutation is not predictive for recurrent pregnancy loss (45,46,67).

Dekker et al (25) observed that 18% of women with severe early-onset preeclampsia had a positive methionine loading test. More recently, the same group found hyperhomocysteinemia in 26%, 11%, 38% percent of normotensive women with placental abruption, fetal death, and fetal growth restriction respectively, compared with an estimated 2-3% in the general population (13). These findings have been further supported by two recent reports (9,18).

In a recent systematic review homocysteine for methylene-tetrahydrofolate reductase was associated with placental abruption (pooled odds ratio 2.3, 95% CI 1.1 to 4.9), spontaneous abortion or recurrent pregnancy loss (pooled odds ratio 3.3, 95% CI 1.2 to 9.9), and preeclampsia (pooled odds ratio 2.6, 95% CI 1.4 to 5.1) (5). Low folic acid, but not vitamin B12 deficiency, was also associated with increased risk for placental mediated complications such as preeclampsia, spontaneous miscarriage, and placental abruption (5).

![Figure 1](image-url)  
*Figure 1. Simplified scheme of methionine-homocysteine metabolism and the most important enzymes and related vitamins (adapted with permission from 5). THF, tetrahydrofolate. Defects in methionine synthase activity, cystathionine B synthase, 5,10-MTHFR lead to decreased level of folate result in homocysteinemia.*

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Prothrombin Gene Mutation (Factor II G20210A Mutation)

Recent studies reported that a function-enhancing mutation in the prothrombin gene (G20210A), present in 2-3% of the general population, is associated with more than 3-fold increased risk of thrombosis (68,69). This mutation is currently considered the second most common identified independent risk factor for venous thrombosis (23). The exact mechanism of increased risk of thrombosis is not fully understood, even though it has been shown that the mutation is associated with increased plasma levels of prothrombin.

Associated Pregnancy Complications

It is unclear whether there is an increased risk of fetal loss in pregnant women with G20210A mutation. Pickerly et al (70) demonstrated no difference in the prevalence of this mutation between women with recurrent pregnancy loss and controls (4.4% vs 4.5%). Likewise, Deitcher et al (71) studied 50 women with first trimester recurrent pregnancy loss and found only one individual (2%) with factor II G20210A mutation. By contrast, Brenner et al (45) found a 2.2-fold increase of recurrent pregnancy loss in women with factor II G20210A mutation compared with controls (95% CI 0.6 to 8.0).

Kupferminc et al (18) identified factor II G20210A mutation in 10% of women with severe pregnancy complications compared with 3% of healthy controls (odds ratio 3.9, 95% CI 1.1 to 14.6). They reported a 2.2-fold increase of severe preeclampsia (95% CI 0.4 to 13.9), 8.9-fold increase of placental abruption (95% CI 1.8 to 43.6) and 4.6-fold increase of fetal growth restriction (95% CI 1.0 to 20.0) (18). Interestingly, G20210A mutation was not identified in any of the women with unexplained stillbirth (18).

Recently, we examined the prevalence of genetic mutation encoding for factor V Leiden, factor II G20210A, C677T of the methylene-tetrahydrofolate reductase in 102 women with severe pregnancy complications and 44 healthy controls. Overall, there was no significant difference in the prevalence of the three genetic mutations between the two groups (18% vs 16%, odds ratio 1.1, 95% CI 0.4 to 2.94). Genetic mutation encoding for factor V Leiden, factor II G20210A, C677T of the methylene-tetrahydrofolate reductase were identified in 2%, 11%, and 5% of women with severe pregnancy complications compared with 3%, 2%, and 2% of controls, respectively.

Antiphospholipid Syndrome

The antiphospholipid syndrome refers to the occurrence of thrombosis, recurrent miscarriage, or both in association with laboratory evidence of persistent antiphospholipid antibodies, either lupus anticoagulants and/or anticardiolipin antibodies (72). It is designated as ‘primary’, when it occurs in isolation, and ‘secondary’, when it arises in association with other diseases, such as systemic lupus erythematosus (73). Antiphospholipid antibodies are autoantibodies against negatively charged phospholipids and approximately 2% of women with a normal reproductive history test positive (74,75). In contrast, 15% of women with recurrent miscarriage have persistently positive tests for either lupus anticoagulant or anticardiolipin antibodies (76), as do 20.9% of those with severe preeclampsia (6), 30.9% of those with late fetal loss (14), and 33% of those with placental abruption (77).

Standardized enzyme-linked immunosorbent assay (ELISA) is used for detection of anticardiolipin antibodies. The detection of lupus anticoagulant depends on its ability to inhibit (prolong) phospholipid dependent in vitro blood clotting. Although activated partial thromboplastin time and kaolin clotting time could be used for detection of lupus anticoagulant, Rai and colleagues (76) found that diluted Russell’s Viper Venom Time (dRVVT) is more sensitive than the other two. Laboratory detection of antiphospholipid antibodies has unacceptably high inter-laboratory variation, which could be, to a certain extent, explained by difference in the type of assays used and the fluctuating nature of the antibodies. Rebar et al (78) reported that, depending on the test kits used, quantitative positively for immunoglobulins G and M anticardiolipin antibodies ranged from 31-60% and 6-50%, respectively. Roberts et al (79) recently reported results of 20 patients with recurrent miscarriage tested simultaneously in two centers for anticardiolipin antibodies. Only three patients tested positive for immunoglobulin M in both centers. However, three patients tested positive in center ‘A’ but were not positive in center ‘B’, and further 14 patients tested negative in center ‘A’ but were positive in center ‘B’ (79). These findings highlight the difficulty of comparing studies that use different assays and urge the standardization of testing (15,80). In addition, false positive results could arise secondary to infection or drug intake (3,80-82).

β2-glycoprotein I, discovered in 1990, is a co-factor that enhances the binding of antiphospholipid antibodies (mainly anticardiolipin antibodies) (83-85). Accordingly, antiphospholipid antibodies are subdivided into two subtypes: β2-glycoprotein I-dependent and β2-glycoprotein I-independent anticardiolipin antibodies (16,85,86). In a prospective study of 1,600 healthy women who were tested for β2-glycoprotein I-dependent and β2-glycoprotein I-independent antibodies at 10 weeks’ gestation, Katano and colleagues, reported that women with a positive test for β2-glycoprotein I-dependent antibodies had 52-fold increased relative risk of fetal death (95% CI 12.7 to 216), an 18-fold increased relative risk of fetal growth restriction (95% CI 4.6 to 74.0), and a 22-fold increased relative risk of preeclampsia (95% CI 5.7 to 85.7), when compared with anticardiolipin negative women (87). In contrast, β2-glycoprotein I-independent antibodies did not show any significant association with adverse pregnancy outcome (87). However, the precise role of β2-glycoprotein I has been disputed by others (88,89).

Some investigators believe that β2-glycoprotein I may be actually the “true antigen” recognized by antiphospholipid antibodies (14,90). In a case-controlled study of 232 consecutive women with a history of late fetal loss (>22 weeks), Gris and colleagues (14) reported that in women with antiphospholipid syndrome, the highest risk of stillbirth was associated with positive anti
2-glycoprotein I antibodies (odds ratio 16, 95% CI 2.0 to 128), followed by anticardiolipin antibodies (odds ratio 6, 95% CI 2.5 to 14) and lupus anticoagulant (odds ratio 2.9, 95% CI 1.1 to 7.5). However, Lee et al (91) found that testing for anti 2-glycoprotein I antibodies in women with recurrent miscarriage, unexplained fetal death, and antiphospholipid syndrome did not identify any additional patients who initially had negative test response for anticardiolipin. Moreover, Franklin et al (92) screened 45 women for anti 2-glycoprotein I antibodies, all of whom had a history of recurrent miscarriage and a confirmed diagnosis of antiphospholipid syndrome (both clinical and laboratory). Only 10 (22.2%) women had positive immunoglobulin G antibodies for 2-glycoprotein I (92). The authors concluded that anti 2-glycoprotein I antibodies are a less sensitive marker for the diagnosis of antiphospholipid syndrome, and that additional testing for anti 2-glycoprotein I antibodies is not justified (91,92).

Associated Pregnancy Complications

Recurrent pregnancy loss is one of the defining diagnostic criteria of antiphospholipid syndrome. It appears that most miscarriages in women with antiphospholipid syndrome occur when fetal heart activity has already been established. In contrast, miscarriages in women with negative antiphospholipid antibodies are usually anembryonic (16). Rai et al (76) examined the prevalence of antiphospholipid antibodies among 500 consecutive women with recurrent miscarriage. They found that 15% of them had persistently positive tests for antiphospholipid antibodies (62% lupus anticoagulants only, 15% IgG anticardiolipin antibodies, 9% immunoglobulin M anticardiolipin antibodies, 14% lupus anticoagulants and anticardiolipin antibodies) (76).

Although there is a general support for the association between mid-trimester pregnancy loss and antiphospholipid syndrome, the potential association with first-trimester pregnancy loss is controversial. MacLean et al (93) reported an increased prevalence of lupus anticoagulant and anticardiolipin antibodies in women with a history of first trimester miscarriage. However, other investigators reported a lack of an association between antiphospholipid antibodies and first-trimester spontaneous miscarriages (94-96).

The exact mechanisms of placental mediated diseases are unknown. Placental infarction and/or thrombosis may play a critical role (97,98), although others were unable to confirm the high frequency of placental infarction (99). Current evidence suggests that antiphospholipid antibodies may interfere with various phospholipid-containing proteins, or complexes, including 2-glycoprotein I, protein C, phospholipase A2, prothrombin, thrombomodulin, and annexin V (100). It is likely that these antibodies bind to endothelial cells and/or interact with platelets and trophoblastic cells (101).

In a prospective study of 860 pregnant women screened for anticardiolipin antibodies before 9 weeks gestation, Yasuda et al (11) observed a significant increase of pregnancy complications in women with positive anticardiolipin antibodies compared with anticardiolipin negative group. They reported a significant increase of spontaneous abortion (relative risk 2.5, 95% CI 1.37 to 4.8), preeclampsia (relative risk 6.2, 95% CI 2.34 to 16.0), fetal growth restriction (relative risk 6.2, 95% CI 2.43 to 16.0), and fetal death before 24 weeks of gestation (relative risk 26.6, 95% CI 2.38 to 298.1) in women with positive anticardiolipin antibodies. Their findings are in agreement with recent reports (6,95,102,103), although others were unable to confirm this association (104,105).

It is estimated that up to 30% of patients with antiphospholipid antibodies will deliver before 34 weeks gestation (106). Iatrogenic prematurity could be due to abnormal fetal heart-rate tracings, severe preeclampsia and/or fetal growth restriction (17,106).

Evidence is accumulating, suggesting that treatment with low dose aspirin and heparin may improve the live birth rate in women with antiphospholipid syndrome, but on-going pregnancies remain prone to complications (16). In an uncontrolled study of 150 women with antiphospholipid syndrome and recurrent miscarriages who were treated with aspirin and heparin, Backos et al (17) reported a high incidence of perinatal complications including gestational hypertension (17%), antepartum hemorrhage (7%), small for gestational age infants (15%), and pre-term labor (24%).

Who Should be Tested?

Routine Testing

There is no evidence to support routine screening of all pregnant women for thrombophilia. Studies of healthy blood donors have demonstrated that thrombophilic gene defects are common and the majority of men and women with mutations in antithrombin III and protein C or protein S deficiency remain asymptomatic (107,108).

Women with Pregnancy Complications

The main controversy is whether asymptomatic women with no thromboembolic history, but history of recurrent pregnancy loss or severe pregnancy complications should be tested in a routine clinical setting. In the absence of randomized clinical trials demonstrating unequivocal benefits of thromboprophylaxis or other interventions, we believe that the answer is no. The exception is testing for antiphospholipid syndrome in women with recurrent pregnancy loss (109) or stillbirths with evidence of fetal thrombosis (110).

Women with Previous Thromboembolism or Strong Family History

Women with a history of deep venous thrombosis or a strong family history of thromboembolism should be tested. About 50% of such women will be found to have a thrombophilic defect and their life-long risk of clinically significant thrombosis is high (47). In symptomatic families with inherited thrombophilia, screening before puberty is recommended. A positive result will provide a warning of the increased thrombotic risk of contraceptive pills and pregnancy for young women with thrombophilia (111-114).
Women with antithrombin III deficiency are at substantial risk of developing thromboembolism during pregnancy (115). They should be offered thromboprophylaxis throughout pregnancy and for a minimum of six weeks postpartum. In addition, infusion of antithrombin III concentrate just prior to delivery should be considered (20,116).

Women with a previous thromboembolic event and confirmed protein C, protein S deficiency, or factor V Leiden mutation require thromboprophylaxis throughout pregnancy using either unfractionated heparin or low-molecular-weight heparin. The activated partial thromboplastin time is unreliable for monitoring of unfractionated heparin in pregnancy due to pregnancy-associated increase in factor VIII (117,118). If low-molecular weight heparin is used, anti factor Xa concentrations offer a better alternative and should be maintained at a level of 0.1-0.2 units/mL 4 hours after the heparin injection (119).

In women with hyperhomocysteinemia consideration should be given to supplementation with 25 mg vitamin B6 and folate 5 mg orally daily before and throughout the pregnancy (61). Leeda et al (119) reported that homocysteine-lowering therapy in hyperhomocysteinemic women who suffered from preeclampsia or fetal growth restriction may reduce the obstetric complications in their subsequent pregnancies. Although there are no randomized trials to support such approach, the recent report of significant beneficial effect of folic acid fortification on plasma folate and homocysteine levels in middle-aged adults is reassuring (120).

Women with antiphospholipid syndrome and a prior history of thromboembolism should receive thromboprophylaxis. Heparin plus low-dose aspirin may provide a better pregnancy outcome than low-dose aspirin alone in women with antiphospholipid antibodies and recurrent miscarriages (17,109,12). Steroids are no longer recommended as a first line therapy for patients with antiphospholipid syndrome without overt lupus, because of the association with significant fetal and maternal morbidity (100).

Asymptomatic carriers of thrombophilia with a positive family history of deep venous thrombosis should be assessed carefully and a decision about thromboprophylaxis should be made after weighing the risks and benefits of prophylaxis. Many clinicians would limit thromboprophylaxis to the third-trimester and/or postpartum period (20). This approach should be questioned, because a meta-analysis of all published studies of deep vein thrombosis during pregnancy and the puerperium showed that more than half of all deep vein thromboses during pregnancy occur during the first and second trimester (122).

**Perspectives**

Future research should focus on two main areas. Firstly, more studies are needed to prove (or disprove) a causative link between thrombophilia and pregnancy complications. In particular the role of placental pathogenic mechanisms require further evaluation as recent reports suggest that placental pathological changes are often non-specific (123,124). Secondly, clinical benefits of thromboprophylaxis or other interventions in women with thrombophilia should be evaluated in large randomized clinical trials. However, genetic polymorphism and ethnic differences may be an important limiting factor in wider clinical usefulness of such studies.

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