Clinical Management of Thrombophilia Related Placental Vascular Complications

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ABSTRACT

Pregnancy is a hypercoagulable state with an increased thrombotic risk throughout gestation and the post-partum period.

Women with thrombophilia may have a further increased risk of placental vascular complications, including, pregnancy loss pre-eclampsia, intrauterine growth restriction and placental abruption.

Preliminary data suggest that maternal antithrombotic prophylaxis may result in improved gestational outcome. Randomized trials are underway and hopefully will optimize maternal and neonatal outcome.
INTRODUCTION

Thrombophilic risk factors are common and can be found in 15-25% of Caucasian populations. Since pregnancy is an acquired hypercoagulable state, women harboring thrombophilia may present with clinical symptoms of vascular complications for the first time during gestation or at the post-partum period.

Data concerning treatment of venous thromboembolism (VTE) in pregnancy has been reviewed in a recent issue of Blood [1]. This review will focus on the clinical evaluation and management of women with thrombophilia related placental vascular complications including fetal loss, preeclampsia, intra-uterine fetal growth restriction (IUGR) and placental abruption (Table I). These complications are the leading cause of maternal and fetal adverse outcome and pause a significant psychosocial impact and economical burden.

Hemostatic changes in pregnancy

In normal pregnancy, there is a marked increase in the procoagulant activity, characterized by elevation of factors VII, X, VIII, fibrinogen and von Willebrand factor which is maximal around term (2). This is associated with an increase in prothrombin fragments (PF1+2) and thrombin–antithrombin complexes (3). There is a decrease in physiological anticoagulants manifest by significant reduction in protein S activity (4) and by acquired activated protein C (APC) resistance (5). The overall fibrinolytic activity is impaired during pregnancy, but returns rapidly to normal following delivery (6). This is largely due to placentald derived plasminogen activator inhibitor type 2 (PAI-2), which is present in substantial quantities during pregnancy (7). D-dimer, a specific marker of fibrinolysis resulting from breakdown of cross-linked fibrin polymer by plasmin, increases as pregnancy progresses (8) Overall there is a 4-10 fold increased thrombotic risk throughout gestation and the post-partum period.


Thrombophilia and pregnancy loss

Case presentation

A 32-year-old with one child age 6 years delivered after normal pregnancy. Thereafter she suffered 3 consecutive pregnancy losses at 8-10 weeks of gestation. Thrombophilia workup revealed APC-SR of 1.8 (normal range > 2.0) and heterozygosity for factor V Leiden mutation. Personal and family history of thrombosis were negative.

Recurrent fetal loss (RFL) is a common problem. Of women at the reproductive age group, 1% to 2% experience three or more losses and 5% experience two or more losses (9). Recurrent fetal loss has a well-established association with certain acquired thrombophilic disorders, such as the antiphospholipid syndrome (10).

A growing body of evidence suggests that hereditary thrombophilia is common in women with RFL (Table II). A case control study in women with the inherited thrombophilia, protein C, protein S and antithrombin deficiencies documented an increased risk for RFL. Forty-two out of 188 pregnancies (22%) in 60 women with thrombophilia resulted in pregnancy loss compared to 23/202 (11%) in controls (OR-2.0; 95% CI 1.2-3.3) (11). In addition, a high incidence of gestational abnormalities was reported in 15 women with dysfibrinogenemia associated with thrombosis. Of 64 pregnancies, 39% ended by miscarriage and 9% by intrauterine fetal death (12). In a recent study, at least one thrombophilic defect was found in 96/145 (66%) of women with RFL group compared to 41/145 (28%) in controls (OR=5.0, 95% CI: 3.0-8.5 p<0.0001) (13). The association of factor V Leiden mutation with pregnancy loss has been recently analyzed by the College of American Pathologists Consensus Conference on Thrombophilia (14,15). At least 16 case-control studies found a high prevalence of (FVL) in women with unexplained recurrent fetal loss (up to 30%) compared to 1% to 10% of control subjects (odds ratios ranging from 2 to 5).
Despite differences in study populations and selection criteria, the results were consistent. No association between FVL and fetal loss was found by six other case-control studies. These latter studies were smaller and mostly by included women with early first trimester fetal losses (which often are due to non-thrombophilia-related factors). Three retrospective cohort studies also found that FVL carriers have a significantly increased risk of recurrent fetal loss. The risk for fetal loss is greater in homozygotes than in heterozygotes with FVL (16) and in female siblings of thrombophilic women with FVL (17). Women with thrombophilia have an increased percentage of losses at later stages of gestation (13). Activated protein C resistance in the absence of the FVL has also been associated with pregnancy loss (13,18).

A recent meta-analysis demonstrated that FVL is associated with early (OR 2.01, 95% CI 1.13-3.58) and late (OR 7.83, 95%, CI 2.83-21.67) recurrent fetal loss (20). Exclusion of women with other pathologies associated with fetal loss strengthens the association with FVL. In this meta-analysis APC-resistance was also associated with early recurrent fetal loss (OR 3.48, 95%, CI 1.58-7.69).

Fetal loss has also been associated with factor II G20210A but not with the MTHFR TT polymorphisms (13,19).

Data on treatment of women with inherited thrombophilia and pregnancy loss are predominantly uncontrolled and include small series of patients treated mostly with low-molecular-weight heparin (Table III). Administration of the LMWH, enoxaparin 20mg/day, to women with primary early recurrent fetal loss and impaired fibrinolytic capacity resulted in normalization of impaired fibrinolysis, conception in 16/20 (80%) and successful live birth in 13/16 (81%) (21).

A recent collaborative study demonstrated the safety of using low-molecular-weight heparin during 486 gestations (22). A successful outcome was reported in 83 (89%) of 93 gestations in women with a history of recurrent pregnancy loss and in all 28 gestations in women who
experienced preeclampsia during a previous pregnancy. A retrospective French study on use of enoxaparin during 624 pregnancies revealed good safety profile (23).

Our group has treated 61 pregnancies in 50 women with thrombophilia who presented with recurrent fetal loss with the LMWH enoxaparin throughout gestation and 4-6 weeks into the postpartum period. Enoxaparin dosage was 40mg/day, except for patients with combined thrombophilia or in case of abnormal Doppler velocimetry suggesting decreased placental perfusion, where the dosage was increased to 40mg bid. Forty-six of the 61 pregnancies (75%) resulted in live birth compared to a success rate of only 20% in these 50 women in prior gestations without antithrombotic therapy (24).

Carp et al (25) reported a cohort study undertaken to assess the effect of enoxaparin on subsequent live birth rate in women with 3 or more consecutive pregnancy losses and hereditary thrombophilia. Live birth rate was higher in women treated with enoxaparin 26/37 (70.2%) compared to 21/48 (43.8%) in untreated patients. The beneficial effect was mainly in primary aborters and in those with five or more miscarriages.

These preliminary results are encouraging. However, the optimal dosage of LMWH is yet unknown and should be determined by prospective randomized trials. Ideally large placebo controlled trials should be advocated. However, there are logistical and ethical difficulties, which limit enrolment to such studies.

LIVE-ENOX is a multi-center study recently conducted in Israel comparing two doses of enoxaparin, 40mg/d and 40mg/every 12 hours given throughout pregnancy, starting at 5-10 weeks and for 6 weeks at the postpartum period to women with thrombophilia and recurrent pregnancy loss (26). The results will be available soon.
In the meantime it is recommended that women with recurrent pregnancy loss and thrombophilia on subsequent gestation should be enrolled in clinical trials or treated on an individual basis.

Accordingly this patient should be offered on subsequent pregnancy to receive LMWH at a prophylactic dose (Enoxaparin 0.5mg/kg or Dalteparin 5000U) starting early after pregnancy is diagnosed and continuing throughout gestation and 6 weeks into the post-partum period. Whether monitoring of anti-Xa levels is of value is still unknown. However, levels of 0.2-0.4U/ml 3 hours post S.C injection are expected in pregnant women who receive prophylactic doses of LMWH.

**Thrombophilia and IUGR**

**Case Presentation**

A 25-year-old woman presented after delivering at 36 weeks of gestation in her first pregnancy a 1500gr newborn. Thrombophilia workup 3 months after delivery was normal except for activated protein C resistance (APC-SR = 1.7, normal ranges > 2.0), with factor V R506Q genotype. Family history was negative for thrombosis.

This patient had an early delivery of a small for gestational age neonate.

Risk factors for IUGR can be of maternal, fetal or placental origin. Among maternal causes are chronic vascular disease, inherited and acquired thrombophilia. Chronic abruption and extensive infraction are among the placental abnormalities.

The association of IUGR and thrombophilia is controversial. An association was demonstrated in women with severe IUGR (**Table II**) but not in milder cases. Martinelli et al (27) studied 63 women with history of IUGR defined as birth-weight under the tenth percentile and 93 parous women with uneventful pregnancies. Among women with IUGR
13% had FVL compared to 2.2% in controls (OR 6.9, 95%CI 1.4-33.5), and 12% had prothrombin mutation compared to 2.2% in controls (OR 5.9, 95%CI 1.2-29.4). In a regression analysis model these thrombophilias were independently associated with IUGR. A later report from the same group (28) tested these mutations in neonates < 2500 grams. Neonates delivered by mothers with FVL or prothrombin mutations accounted for 30% of newborns weighting < 1000g, 18.7% of those ranging from 1001-2499g and only 9.5% among babies weighting ≥ 2500g. Overall 27.6% neonates of mothers with the mutations weighed less than 2500g compared to 13.9% in neonates of mothers without mutations (OR 2.4, 95% CI 1.5-3.7).

Recently, Infante-Rivard et al (29) did not find an association between thrombophilic mutations and intrauterine growth restriction less then 10th percentile. In this study the prevalence of thrombophilia in mothers of 493 newborns with IUGR and 472 controls did not differ significantly. However, one third of the studied population were not Caucasians and the degree of IUGR was mild, with mean birth weight of 2393 ± 606 grams, and 83% of newborns were delivered at 36-40 weeks gestation. In contrast, in the study by Kupferminc et al (30) the mean birth weight was 1387±616 grams and mean gestational week was 33±4.0. Similarly, Martinelli et al (26) reported a mean gestational week at delivery of 35 ± 3 and a mean birth weight of 1584±586 grams. It is therefore suggested that these studies are dealing with non-comparable fetal and neonatal populations with different clinical relevance.

Data on antithrombotic prophylaxis for IUGR at index pregnancy and on subsequent gestations is limited. However, in view of the risk for recurrences of other gestational complications including IUGR prophylaxis can be considered. This case can be managed with LMWH at a prophylactic dose (Enoxaparin 0.5mg/kg or Dalteparin 5000U) once daily throughout gestation, and for 6 weeks in the post-partum period. This regimen may also be useful for prevention of other vascular complications.
Case presentation

A 36 year old woman presented on her second gestation at 25 weeks with preeclampsia which progressed rapidly into HELLP syndrome and necessitated cesarean delivery at 26 weeks of a 700 gr neonate. The newborn had a complicated course including necrotizing enterocolitis at the neonatal intensive care unit. Thrombophilia workup revealed heterozygosity for factor II G20210A mutation. Her first gestation ended by miscarriage at 10 weeks. Family history was negative for thrombosis.

This patient had complications on gestations, a miscarriage and severe early onset preeclampsia with HELLP syndrome.

Preeclampsia can be found in 3-7% of pregnancies and is a leading cause of maternal and fetal life-threatening complications. In preeclampsia the placental vasculature fails to become a high-volume, low-pressure system, which is the earliest difference that can be detected between pre-eclamptic and normal pregnancies. Widespread deposition of fibrin and vascular damage normally occur in hypertensive disorders of pregnancy, suggesting an activation of the coagulation cascade in this condition (31). Recent reports suggesting that VEGF is decreased in preeclampsia (32,33) may be relevant for development of novel therapeutic modalities for this disorder.

The association of preeclampsia and thrombophilia is controversial. A number of case control studies have demonstrated an association while other studies have refuted this occurrence (Table II). An association between the presence of FVL and a history of severe forms of preeclampsia was reported (34).

Kupferminc et al found that the prevalence of thrombophilia in 110 women with severe obstetric complications was 65% compared to 18% in 110 controls (30). Women with
obstetric complications had also significantly higher incidence of combined thrombophilias. The results showed a higher prevalence of the thrombophilic polymorphisms, FVL, factor II G20210A and MTHFR677 TT in women presenting with preeclampsia (30). In a sample of 140 Italian women with a history of gestational hypertension, with or without significant proteinuria, a significantly higher prevalence of thrombophilic risk factors was documented regardless of the presence of proteinuria (35). Logistic regression showed that FVL and factor II G20210A mutations were independently associated with occurrence of gestational hypertension.

Other studies failed to find an association between a common genetic risk factor for thrombosis and the occurrence of preeclampsia (36). However, these studies seem to differ in selection of controls and in ethnic backgrounds.

A recent meta-analysis has demonstrated an association with FVL, and factor II G20210A only in women with severe early onset of preeclampsia (37). HELLP syndrome is a severe form of preeclampsia manifesting disseminated platelet aggregation and liver dysfunction, necessitating early emergent termination of pregnancy. This syndrome has been associated with thrombophilia particularly with the factor V Leiden mutation (38).

In the eighties the potential benefit of aspirin in prevention of preeclampsia has been raised and refuted. To date there are no placebo controlled trials on prevention of preeclampsia at subsequent gestation with LMWH. Small-uncontrolled studies have suggested a benefit in outcome of subsequent gestations after antithrombotic prophylaxis (Table III) (39-41).

However, the risk in this woman is high and therefore counseling should take into account her age, the severe obstetric history and risks of recurrence on subsequent gestation. Prophylaxis during pregnancy should probably include LMWH at a moderate to high prophylactic dose
throughout gestation and the post-partum period aiming for anti-Xa levels of 0.4-0.6U/ml 3 hours post injection. Whether aspirin should be added is currently unknown.

**Combined Thrombophilic risk factors**

**Case presentation**

A 22-year-old woman with one previous pregnancy loss at 10 weeks. She is currently on her 6th week of gestation. Family history includes DVT in her father at 35 years and pulmonary embolism in his brother at the age of 40 years.

Thrombophilia workup (3 months after the first pregnancy loss) revealed antithrombin activity of 60U/dl and antigenicity of 65U/dl (normal values 80-120 U/dl), homozygosity for MTHFR 677TT and hyperhomocysteinemia - 20µmol/L. (normal range 5-12 µmol/L)

**Antithrombin deficiency**

Antithrombin deficiency is an uncommon severe thrombophilia often manifest clinically by gestational vascular complications with a significant increased maternal and fetal risks. The risk is estimated to be increased by 100-150 folds, which translates to clinically overt DVT in 7% of antithrombin deficient pregnant women and up to 40% in case of severe familial DVT (42-44).

Furthermore, antithrombin deficiency has been associated with other pregnancy complications including pregnancy loss and late gestational complications (11).

**Hyperhomocysteinemia and MTHFR 677TT**

Homocysteine levels decrease in pregnancy by 50%. Gestational vascular complications can be associated with hyperhomocysteinemia documented in 26% of women with placental abruption, in 11% of cases with intrauterine fetal death and in 38% of women
delivering babies whose birth weight were below the fifth percentile compared with an estimated 2-3% in controls (45). Likewise, hyperhomocysteinemia was documented in 26/84 (31%) women with previous placental infarcts or abruption compared to 4/46 (9%) in controls (46). In the Hordaland homocysteine study, which is the largest performed to date; plasma homocysteine levels were evaluated in 5883 women with 14,492 pregnancies (47). The study demonstrated that when comparing the upper with lower quartile of plasma homocysteine, the adjusted risk for preeclampsia was 1.32 (95% CI 0.98-1.77), for prematurity 1.38 (95% CI 1.09-1.75), for very low birth weight 2.01 (95% CI 1.23-3.27), and for stillbirth 2.03 (95% CI 0.98-4.21).

In a recent meta-analysis, Nelen et al (48) reviewed 10 case control studies, which examined the association of RFL. (Table II) and hyperhomocysteinemia and reported a 3-4 fold increased risk, while in 6 studies the odds ratio for homozygosity for MTHFR were not significant. These data suggest that while HHC is a risk factor for RFL, homozygocity for MTHFR as a solitary thrombophilic defect is not. However, testing for MTHFR 677TT may be of value in women with relative decreased folate and vitamin B12 levels commonly acquired during pregnancy and for identifying women with a combination of MTHFR 677TT and additional thrombophilia who may be at higher risk during gestation (49).

Indeed, combinations of thrombophilic risk factor may further increase the risk for RFL. The EPCOT study documented the highest odds ratio for stillbirth (OR=14.3, 95% CI 2.4-86) in patients with combined thrombophilic defects (50).

Combined thrombophilic defects were documented in 31/145 (21%) of women with pregnancy loss compared to 8/145 (5.5%) in controls (OR=5.0, 95% CI: 2.0-11.5 P<0.0001)(13). In the NOHA-5 study, placental pathological vascular findings were
documented in 88% of women with combined thrombophilia, and in 100% of those with a combination of any thrombophilia and MTHFR 677TT (49).

While MTHFR TT by itself is not a risk factor for maternal thrombosis or pregnancy loss, it can lead to a relative hyperhomocysteinemia. This is particularly true in pregnancy when maternal folic acid and vitamin B12 levels may decrease due to fetal use.

Therefore, in this patient with severe combined thrombophilia ample intake of folate and vitamin B12 is advocated. LMWH should be administered twice daily starting at a high prophylactic dose (Enoxaparin 0.5mg/kg or Dalteparin 5000U every 12 hours) aiming for Anti-Xa level of 0.4-0.6 U/ml 3 hours post injection.

Close monitoring of fetal growth and estimation of placental perfusion by Doppler velocimetry are advocated. Prophylaxis should be given throughout gestation and the post-partum period.

Inherited Thrombophilias and Abruptio Placentae

Case presentation

A 30 years old woman presented with placental abruption at 27 weeks gestation with delivery by emergent cesarean section of an 800gr neonate. Thrombophilia workup revealed heterozygosi for factor II G20210A.

Placental Abruption is uncommon devastating clinical presentation occurring in 0.5% of gestations but carries a high fetal mortality and significant maternal risk. Risk factors for placental abruption include preeclampsia, prior abruption, sudden uterine decompression, chemical teratogens external trauma and uterine malformations (51). A potential association with thrombophilia is suggested by a number of studies (Table II).
van der Molen et al (52) found that the prothrombotic risk factors for placental vasculopathy are decreased levels of APCR and protein C, elevated homocysteine, MTHFR TT and particularly combinations of these factors.

Wiener-Megnagi et al (53) studied 27 women who had abruptio placentae and 29 control subjects matched for age, parity, and ethnic origin. 63% of case patients had an activated protein C ratio ≤ 2.5, compared with 17% of control subjects with OR of 8.16 (p = .001). 8 of 15 patients were found to have the factor V Leiden, compared with 1 heterozygote in the controls (3.4%). Thrombophilia was found in 70% of 20 women with abruptio placentae (54), the OR for factor II G20210A mutation was 8.9 (95% CI 1.8-43.6), whereas the OR for factor V Leiden were 4.9 (CI 1.1-17.4). An increased prevalence in first-degree relatives for venous thrombosis in women with placental abruption indicates a higher prevalence of thrombophilia (54). Based upon these data and in the absence of prospective clinical trials on subsequent gestation these women may be offered prophylaxis with LMWH (Enoxaparin 0.5mg/kg or Dalteparin 5000U) throughout gestation and the post partum period.

**Asymptomatic factor V Leiden carrier**

**Case presentation**

A 27-year-old asymptomatic woman was found to be heterozygote for factor V Leiden (FVL) mutation as a result of familial workup performed after her father had deep vein thrombosis. She is now planning her first pregnancy. How would you consult her?

A recent Canadian survey suggests that 54% of obstetricians in Canada would treat this patient with some form of antepartum prophylaxis (55). However, this is not supported by solid data. In fact, the risk for VTE during pregnancy in asymptomatic woman heterozygote for factor V Leiden is around 0.2-0.5% (56). The risk may increase somewhat in the presence of
significant familial history of thrombosis but is still too low to confer the need for antepartum prophylaxis (57). The risk for placental vascular complications on first pregnancy in women heterozygote for factor V Leiden is not significantly increased compared to controls and therefore thromboprophylaxis in not recommended. Therefore this woman should be managed by clinical surveillance (58). In women with severe or combined thrombophilia the risk is increased and therefore antepartum thromboprophylaxis should be considered.

Unresolved Issues

Fetal Genotype

While there have been reports that fetal thrombophilia is important for the outcome of pregnancy (59), there are a number of reasons to suggest that this may not be the case. First, most thrombophilic polymorphisms are mild risk factors for gestational vascular complications (GVC) and gestational VTE. Second, thrombotic changes are noted mainly on the maternal side of the uteroplacental unit. Third, LMWH that does not cross the placenta is beneficial. Thus, unless there is a severe thrombophilic defect (i.e., homozygous protein C deficiency), fetal thrombophilic state is probably not a major contributor for GVC or VTE.

Does aspirin have a role?

The role of aspirin, if any, in the setting of thrombophilia and vascular gestational abnormalities remains to be confirmed. Currently, as an extrapolation to studies with UFH (60) in patients with antiphospholipid syndrome, aspirin is given along with LMWH. However, whether aspirin has an added value to UFH or LMWH alone has not been evaluated.
**Women with unexplained pregnancy loss**

When evaluation for current known thrombophilia is negative, the idea is that yet undiscovered thrombophilia may be implicated in the placental thrombotic changes that can be found in women with GVC without thrombophilia. Following preliminary experience with antithrombotic therapy in these women, prospective randomized multi center trials are currently underway.

**Future Perspectives**

There are a number of issues in this field that are probably need to be addressed.

First, as for now 30-50% of vascular gestational pathologies cannot be accounted for by currently available tests for thrombophilia. Whether other genetic or acquired thrombophilia will be found to play a role remains to be determined. Preliminary observations claim that the PAI-1 4G/4G polymorphism (61) genes and polymorphisms at the thrombomodulin and endothelial protein C receptor (62,63) may be associated with RFL. Circulating microparticles identified by flow cytometry and have recently been suggested to play a role in women with RFL (64). While the involved mechanism has not been established it is intriguing to speculate whether anti- thrombotic strategies will be of value in this setting (65).

Second, In view of the potential association of thrombophilia and RFL, and the high prevalence of thrombophilia in Caucasian populations, issues of screening are raised. As complete thrombophilia work-up is currently elaborate and costly, screening tests are highly warranted. One such potential assay is the Protein C Global test, which in a preliminary study was found to be abnormal in the majority of women with RFL and could also identify women with RFL who did not have any other thrombophilic defect (66).

Third, the pathogenetic mechanisms responsible for placental vascular pathologies in women with thrombophilia have not been elucidated and it is yet unknown why certain women with
thrombophilia express vascular gestational pathologies while others do not. It is possible that this may relate to local factors affecting coagulation, fibrinolysis and vascular tone at the level of placental vessels.

Finally, the role of antithrombotic modalities deserves prospective clinical trials, in order to improve results in a large population of women who currently experience poor gestational outcome. Future trials should focus on efficacy and safety of tailored therapy for specific thrombophilic polymorphisms in a particular gestational complications setup.
Table I: Pregnancy complications – Definitions

<table>
<thead>
<tr>
<th>Pregnancy loss</th>
<th>weeks of gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embrionic loss</td>
<td>between 5-10</td>
</tr>
<tr>
<td>Fetal loss</td>
<td>after 10</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>Before 20</td>
</tr>
<tr>
<td>IUFD (still birth)</td>
<td>after 20</td>
</tr>
<tr>
<td>First trimester loss</td>
<td>5-12</td>
</tr>
<tr>
<td>Second trimester loss</td>
<td>13-24</td>
</tr>
<tr>
<td>Third trimester loss</td>
<td>after 24</td>
</tr>
</tbody>
</table>

**Placental abruption** – premature separation of a normally located placenta prior to delivery of the fetus.

**Preeclampsia** - pregnancy induced or aggravated hypertension that may be associated with proteinuria and/or other manifestations.

**Intrauterine growth restriction (IUGR)** - A fetus small for gestational age [< 10 percentile or < 3 percentile (severe IUGR)].
Table II: Association of Thrombophilia with Placental Vascular Complications

<table>
<thead>
<tr>
<th></th>
<th>Miscarriages</th>
<th>IUFD</th>
<th>Severe IUGR</th>
<th>Severe Pre-eclampsia</th>
<th>Placental Abruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin def.</td>
<td>I + ref (11,50)</td>
<td>I + ref (11,50)</td>
<td>II +</td>
<td>II +</td>
<td>III+</td>
</tr>
<tr>
<td>Protein C def.</td>
<td>I + ref (11,50)</td>
<td>I + ref (11,50)</td>
<td>ND</td>
<td>ND</td>
<td>III+</td>
</tr>
<tr>
<td>Protein S def.</td>
<td>I ref (11,13,50)</td>
<td>I + ref (11,50)</td>
<td>II+ 45</td>
<td>II +45</td>
<td>III +45</td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>II + ref (12)</td>
<td>II + ref (12)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>APC-Resistance</td>
<td>I + ref (13,18,19)</td>
<td>I + ref (13,18)</td>
<td>II +</td>
<td>II +</td>
<td>II + ref (53)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>I + ref (13-17,20)</td>
<td>I+ ref (13-7,20)</td>
<td>II + ref (28-30)</td>
<td>II+ ref (30,34-38)</td>
<td>II + ref (53,54,30)</td>
</tr>
<tr>
<td>MTHFR 677TT</td>
<td>I – (48)</td>
<td>I –(45)</td>
<td>II – ref (45,46,47)</td>
<td>II–(35,36,45,46,47,37)</td>
<td>II -</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>I + ref (47,48)</td>
<td>I+ ref (45,47)</td>
<td>II+ ref (45,47)</td>
<td>II +</td>
<td>II+ ref (45,46, 52)</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>I +</td>
<td>I +</td>
<td>II+ ref (28-30)</td>
<td>II + ref (29,36,38,37)</td>
<td>II+ ref (30,54)</td>
</tr>
<tr>
<td>Antiphospholipid Antibodies</td>
<td>I+(13,49)</td>
<td>I+(13,49)</td>
<td>II+(30)</td>
<td>II +(30)</td>
<td>II +(30)</td>
</tr>
<tr>
<td>Combined Defects</td>
<td>I+ (13,49,50)</td>
<td>I+(30,13,49,50)</td>
<td>II+(30)</td>
<td>II +(30)</td>
<td>II+(30)</td>
</tr>
</tbody>
</table>

**Level I:** The recommendation is based on 1 or more well-designed prospective studies or 2 or more well designed retrospective studies.

**Level II:** The recommendation is based on retrospective studies that reach consensus.

**Level III:** The recommendation is based on isolated anecdotal studies and/or the consensus of expert practitioners.

+ Association present
- Association not present

**ND:** No Data
**Table III: Observational Studies on Prevention of Poor Gestational Outcome in Carriers of Thrombophilia**

<table>
<thead>
<tr>
<th>Pts (n)</th>
<th>Type of Thrombophilia</th>
<th>Obstetric history</th>
<th>Treatment</th>
<th>Live birth with normal outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Inherited and acquired</td>
<td>RFL</td>
<td>Enoxaparin (+ASA for APS)</td>
<td>46/61 (75%)</td>
<td>Brenner (24)</td>
</tr>
<tr>
<td>25</td>
<td>Factor V Leiden or Factor IIg20210A</td>
<td>RFL, preeclampsia IUGR</td>
<td>UFH or LMWH or ASA</td>
<td>29/31 (93%)</td>
<td>Grandone (41)</td>
</tr>
<tr>
<td>33</td>
<td>Not specified</td>
<td>Pregnancy complications</td>
<td>Enoxaparin 40mg+ASA</td>
<td>30/33 (91%)</td>
<td>Kupferminc (40)</td>
</tr>
<tr>
<td>26 patients Vs 19 controls</td>
<td>Inherited and acquired</td>
<td>Pregnancy complications</td>
<td>Enoxaparin 40mg+ASA</td>
<td>Higher birth weight in LMWH group</td>
<td>Riyazi (39)</td>
</tr>
<tr>
<td>37 patients vs 48 controls</td>
<td>Inherited</td>
<td>RFL</td>
<td>Enoxaparin 40mg</td>
<td>70% vs 44% in controls</td>
<td>Carp (25)</td>
</tr>
</tbody>
</table>

**RFL** – recurrent fetal loss  
**APS** – Antiphospholipid syndrome  
**IUGR** – intra uterine growth restriction
Reference:


Clinical Management of Thrombophilia Related Placental Vascular Complications

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