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# Combined Thrombophilia and Obstetric Complications

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**Abstract:** Gestational vascular complications are a major cause of maternal and fetal morbidity. A growing body of evidence suggests significant correlation of inherited and acquired thrombophilia with pregnancy loss, pre-eclampsia, eclampsia, placental abruption, intrauterine growth restriction (IUGR), and intra uterine fetal death (IUFD). Placental pathological findings in women with thrombophilia are characterized by thrombosis and fibrin deposition to a greater degree than in normal pregnancy [1]. The term Combined Thrombophilia is used when more than one prothrombotic conditions exist at the same time. As per definition any added prothrombotic diathesis promotes pregnancy to a combined thrombophilic state [1, 2]. Thrombophilic risk factors are common and can be found in 15% to 25% of Caucasian population. The combination of prothrombotic risk factors is not uncommon. 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 postpartum period [3, 4]. Combined thrombophilia also exists when inherited and/or acquired prothrombotic factors are pooled. Every combination carries a different risk of thrombosis. A scoring system, which is composed of four major categories: obstetrical history, previous thromboembolic events, family history and type of thrombophilia, can help us to stratify universally the thrombotic risk during pregnancy and peripartum and administer the appropriate antithrombotic treatment.

**Keywords:** Thrombophilia, pregnancy loss, placental abruption, IUGR, IUFD, IVF.

## BACKGROUND

Pregnancy is considered to be an acquired hypercoagulable state due to increased levels of coagulation factors, decreased levels of anticoagulants and decreased fibrinolytic activity. The gradual increase in hypercoagulability during normal pregnancy predisposes to venous thromboembolism (VTE), and to gestational vascular complications, including recurrent pregnancy loss, intrauterine- growth restriction (IUGR), eclampsia, pre-eclampsia and placental abruption. These adverse pregnancy outcomes affect up to 15% of gestations and are the major cause of maternal and fetal morbidity and mortality [3]. In one study, at least one thrombophilic defect was found in 96/145 (66%) of woman with recurrent fetal loss compared to 41/145 (28%) in controls (or=5.0, 95/5 ci: 3.0-8.5 p <0.0001) [4].

Inherited thrombophilia is common and can be found in 15% to 25% of Caucasian populations. Thus, a combination of thrombophilic risk factors is not rare and can be detected, regarding Israel, in up to 5% of women with pregnancy loss [4, 5].

Factor V Leiden is the most common inherited mutation that is associated with increased risk of VTE. Other commonly inherited thrombophilia type is the prothrombin (FII G20210A) mutation but also the C677T polymorphism in the methylenetetrahydrofolate- reductase gene, which results in a thermolabile variant of the enzyme predisposing to hyperhomocysteinemia. However, the most thrombogenic inherited thrombophilia is the rarer antithrombin deficiency, with an estimated thromboembolic risk of 60% during pregnancy and 33% during the puerperium [6].

An individual with multiple thrombophilia polymorphisms faces even greater thrombotic risk compared to non combined thrombophilias. For example, factor V Leiden existing concomitantly with protein C or protein S deficiency, or factor V Leiden or prothrombin 20210A paired with hyperhomocysteinemia carry relative risks of venous thrombosis greater than any of these factors alone. Regarding patients with a history of thrombotic disease from the European Prospective Cohort on Thrombophilia (EPCOT) study, the highest odds for a stillbirth (odds ratio [OR], 14.3; 95% CI, 2.4–86.0) occurred in women with combined thrombophilia defects [4, 7, 8].

Multiple inherited thrombophilias also may interact at the maternal-fetal interface. Consistent with Mendelian inheritance, the fetus will inherit 1 of the maternal alleles at each gene of the clotting-cascade proteins. Chronologically, the fetal arterial supply is established as maternal spiral arteries perfuse the intervillous spaces, with maternal and fetal blood. Blood supply of the placenta is present as early as 3 to 4 weeks after conception. Histologically, evidence of placental ischemia can be found on either the maternal or fetal side. Initial study of factor V Leiden from spontaneous miscarriages suggests a slight skewing toward increased fetal inheritance of the maternal polymorphism, suggesting a further contributory role of the fetus to overall risk [7, 9]. Combined thrombophilia (two or more thrombophilic factors) was significantly higher in women who have had repeated IVF failure as compared with the two control groups (35.6 versus 4.4 and 3%) (P<0.0001). Thrombophilia has been implicated in

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IVF-embryo transfer implantation failure. Women with repeated IVF-embryo transfer failures should be screened for thrombophilia [10].

Homozygosity for MTHFR is common world wide with estimated 10-25% prevalence among various ethnic backgrounds. Thus combinations of other thrombophilic risk factors with homozygosity for MTHFR are not unusual. In the Nimes obstetrics and Hematologists Study 5 (NOHA5), placental pathologic vascular findings were documented in 88% of women with combined thrombophilia and in 100% of those with combination of any thrombophilia and MTHFR 677TT [4, 9]. In another study Four women (1%) had the FV Leiden/MTHFR T677T double genotype and two women (0.5%) had the FII G20210A/MTHFR T677T double genotype. Although the small number of cases of combined inherited thrombophilia, it seemed that the presence of FV Leiden/MTHFR T677T double genotype increases the risk for placental abruption [11].

The prevalence of factor V Leiden in general population is 5-9%, and it is present in 20-40% of non-pregnant patients with thromboembolic events. This risk is much higher in women who are homozygotic, but fortunately this condition is rare [6]. Combination of factor V Leiden with familial antiphospholipid syndrome or factor V Leiden and hyperhomocysteinemia were reported to result in thrombosis and recurrent fetal loss [12, 13].

FII G20210A mutation has a prevalence of 2-3%. Although less frequent than factor V Leiden, it is detected up to 17% of pregnant patients with thromboembolism. In a series of 84 pregnancies in 47 women with combined thrombophilia (factor V Leiden and FII G20210A), the relative risk of pregnancy-related VTE was 2.9, in comparison with women carrying only the FII G20210A mutation. Interestingly, in the group with combined thrombophilia, 17.8% of the patients who were not given any prophylaxis developed VTE during pregnancy or the Puerperium. Compared with women with only the FII G20210A mutation, women with combined thrombophilia had a threefold greater risk of VTE [6].

Proteins C and S are natural anticoagulants. Women of reproductive age who are deficient in protein C, protein S or ATIII have a three times higher risk of thromboembolic disease than do men of the same age [14]. A higher risk of spontaneous abortion in women with these deficiencies has been reported. Since protein C deficiency can affect 10 to 15% of young individuals with recurrent venous thrombosis and protein S deficiency occurs in 2.2% of patients with venous thrombosis, Cousto *et al.* investigated whether Thrombosis at an implantation site could lead to recurrent abortion in women with these deficiencies. The prevalence of protein C, protein S and ATIII definciencies did not differ between the groups studied and hence the hypothesis was not confirmed. The numbers of patients with a deficiency of either antithrombin, protein C, or total protein S were too small to allow an accurate assessment of the associated risk of VTE [15]. However, researchers claim that association does not confer causation of pregnancy complications by thrombophilic polymorphisms [16].

The detection of anti phospholipid antibodies (aPL) such as anti cardiolipin (ACA) and lupus anticoagulant (LA) seems to be higher in the first trimester in women who have anti-phospholipids syndrome (APS), but positive transient results have been detected in women without APS. APS and implantation site thrombosis can justify 5 to 10% of RFL although the mechanism of action is not elucidated completely. It is possible that an inherited factor that alone would not strongly predispose a woman to thrombosis could, when associated with an acquired factor, initiate the thrombotic process. The association between heterozygous C677T mutation in the MTHFR gene and ACA may increase the likelihood of thrombosis expression. It is known that persistently elevated serum levels of ACA are associated with RFL. Positive results for ACA may be the initiation point for a thrombotic process [15]. Forastiero *et al.* investigated thrombophilic genotypes that are associated with APS. Among 105 aPL patients, 69 were diagnosed as having definite APS whereas the remaining 36 comprised the non-APS group. There were 2 heterozygous carriers of FVL among patients with APS, one with a history of recurrent deep venous thrombosis and the other with cerebral arterial thrombosis. Among aPL patients carrying the FII G20210A, 6 had definite APS and 1 belonged to the non-APS group (all heterozygotes). This Prothrombin variant was present in two APS patients, one of whom had experienced recurrent intrauterine fetal death and the other, four spontaneous abortions. Four out of 6 APS patients bearing the FII G20210A experienced vascular thrombosis, two a history of venous and 2 arterial thrombotic events. In two cases, thrombosis recurred. Frequencies of FVL, MTHFR-677TT and the 4G/4G genotype of the PAI-1 were not different either between the aPL groups and normal controls or between APS and non-APS groups. However, FII G20210A was significantly more frequent in APS patients than in normal controls (OR 4.67, p=0.02). In addition, this genetic variant was more prevalent in patients with APS (8.7%) than in those belonging to the non-APS group (2.8%) although the difference did not reach statistical significance. A separate analysis of the presence of gene polymorphisms for clinical manifestations (venous thrombosis, arterial thrombosis and obstetric complications) was not perform because of the limited number of patients in each subgroup. Data showed that a higher proportion of patients diagnosed as having definite APS have the FII G20210A variant combined with the 4G/4G genotype of the PAI-1 than patients with aPL without clinical features of APS and healthy controls. Thus, it is likely that when potential genetic risk factors exert their action simultaneously, these effects may interact and the final event may exceed the sum of the separate actions. This could be particularly relevant in patients with additional acquired factors, such as aPL syndrome. The presence of prothrombotic genetic defects might influence the development of APS-related clinical features in a subpopulation of patients with aPL. Therefore, testing for heritable thrombophilia would be important in order to identify aPL subjects with an increased risk of APS. However, larger cohorts of aPL patients will have to be studied in order to confirm these findings [17].

## COMBINED THROMBOPHILIA AND THE SCORING SYSTEM FOR THROMBOSIS IN PREGNANCY

Currently, there are no clear criteria or guidelines for prediction and prevention of adverse pregnancy outcomes. In fact, the management of thrombophilic pregnancies depends

largely on clinical judgment. Sarig *et al.* proposed a novel scoring system for women with thrombophilia including standardization to evaluate severity of pregnancy outcomes, thrombotic history and type of thrombophilia [3].

The scoring system is composed of four major categories: obstetrical history, previous thromboembolic events, family history and type of thrombophilia. The inquiry includes information on history of venous thromboembolism (deep vein thrombosis, pulmonary embolism, splanchnic, cerebral or other thromboses), major stroke, and the underlying clinical background which led to these events (idiopathic, pregnancy, use of oral contraceptives, immobilization, etc.). Higher scores are given to more significant thrombotic events and the nature of thrombotic and idiopathic onset. In addition, the patient is questioned for the existence of positive family history regarding thrombosis or gestational vascular complications [3].

Inherited thrombophilic traits are scored according to reported prothrombotic tendency during pregnancy with antithrombin and homozygous factor V Leiden scored highest as single traits. Combined thrombophilia also has a higher score, and is sub-classified as "combined moderate" (i.e. heterozygous for both factor V Leiden and prothrombin G20210A mutations) and "combined severe" (i.e. strong lupus anticoagulant and homozygous for factor V Leiden or Antithrombin deficiency). The total score is calculated by summing up the scores of the four categories of thrombosis, obstetrical, family histories and thrombophilia. Based upon the score achieved, pregnancy risk for an individual woman may be stratified into four levels of risk: low (score $\leq$ 5), intermediate (score 6-10), high (score 11-14) and extremely high (score $\geq$ 15).

## SAFETY OF LMWH PROPHYLAXIS DURING PREGNANCY

Greer *et al.* evaluated safety and efficacy of LMWH in 2,800 LMWH treated pregnancies [18]. The main indications were prophylaxis of VTE and prevention of pregnancy loss. The rate of bleeding complications was low and thrombocytopenia was rare, with no cases of heparin-induced thrombocytopenia. Likewise, clinically significant osteoporosis was extremely rare. Live birth rates were 85% to 96%, depending on the indication for treatment [18]. A good safety profile on the use of enoxaparin during 624 pregnancies was also documented in a retrospective French study [19].

While the evidence level is low due to lack of large clinical trials, expert opinion is based on available literature and common practice. The optimal dosage of LMWH is yet unknown and should be determined by prospective randomized trials. Ideally large placebo-controlled trials should be advocated. Logistic and ethical difficulties, however, limit such an approach.

LIVE-ENOX is a multicenter, prospective, randomized study comparing two doses of enoxaparin, 40 mg/d and 40 mg/every 12 hours, in women with thrombophilia and a history of pregnancy loss [20, 21]. Of the 180 women enrolled, live birth rate before the study was only 28%, but during the study, live birth rates were 84% for the 40 mg/d group and 78% for the 80 mg/d group. Late gestational complications decreased after enoxaparin treatment. The incidence of preeclampsia in the treated pregnancies was 3.9% compared with 10.5% in previous gestations. Both doses of treatment seemed to be safe and well tolerated. Postpartum bleeding (1.1% of women in each group) and enoxaparin-related allergic local skin reactions at the injection sites were observed in a small number of women (2.2% and 3.3% of those receiving 40 mg/day and 80 mg/day, respectively). Prophylaxis with enoxaparin (40 mg/day or 80 mg/day) is thus safe and effective for improving pregnancy outcome and potentially for reducing late pregnancy complications in thrombophilic women who have a history of pregnancy loss.

## MONITORING OF LMWH THERAPY DURING PREGNANCY

Since LMWHs inhibit preferentially FXa and to a lower extent thrombin and activated partial thromboplastin time, anti-Xa assays have been developed and validated to determine their anticoagulant effect. Several studies performed demonstrated lower than expected anti-Xa activity levels during pregnancy compared to the non pregnant state. A recent study investigated the modulation of systemic hemostatic parameters by enoxaparin in women with recurrent pregnancy loss and suggested monitoring LMWH prophylaxis effect during pregnancy. Plasma Anti-Xa levels at 10-15 weeks gestation where higher (0.39+/-0.38 u/ml) in the successful pregnancy outcome group compare to the abortion group. Prophylactic Anti-Xa activity levels (0.28+/-0.13 u/ml) where documented from 15 weeks if gestation until delivery in the successful pregnancy outcome group. Thus, LMWH prophylaxis during pregnancy enables modulation of systemic hemostatic parameters *via* inhibition of factor Xa and increase in plasmatic total free TFPI level [3]. For the vast majority of patients, LMWH have proved to be effective and safe without the need for anticoagulant monitoring. However, the need to adjust LMWH prophylaxis to the weight of the pregnant woman or to monitor LMWH treatment during pregnancy remains controversial [3].

Our group studied the modulation of systemic hemostatic parameters by LMWH in 87 pregnancies of women participating in the LIVE-ENOX trial [20, 21]. The control group included 40 women with normal pregnancies. Out of the 87 LMWH treated pregnancies, successful pregnancy outcome with live newborn was recorded in 70 (80.5%) women, without correlation to enoxaparin dosage. Seventeen women (19.5%) suffered pregnancy loss at 16±7 (6-32) weeks of gestation. Anti-Xa levels at 10-15 gestation weeks were higher (0.39±0.38 u/ml) in the successful pregnancy outcome group compared to the group with the miscarriages (0.22±0.2 u/ml). Prophylactic anti-Xa levels (0.28±0.13 u/ml) were achieved from 15 week of gestation until delivery in the live born group, without significant differences between gestational ages or LMWH dosages. A significant increase in anti-Xa and tissue factor pathway inhibitor (TFPI) levels ($P<0.001$) was achieved after beginning of LMWH prophylaxis in the successful pregnancy outcome group but not in the miscarriage group. These results suggest that plasma levels of anti-Xa activity and TFPI may help to predict the outcome in LMWH treated pregnancies [3].

## CONCLUSIONS

Pregnancy increases the thrombogenic potential of all thrombophilic disorders inherited or acquired. The different Combined thrombophilia are sub-classified as "combined

moderate" (i.e. heterozygous for both factor V Leiden and prothrombin G20210A mutations) and "combined severe" (i.e. strong lupus anticoagulant and homozygous for factor V Leiden or Antithrombin deficiency). The more severe the blend is, the highest anti-Xa is required. The presence of prothrombotic genetic defects might influence the development of APS-related clinical features in a subpopulation of patients with aPL. Therefore, testing for heritable thrombophilia would be important in order to identify aPL subjects with an increased risk of APS [17].

Last but not least, the role of anti-thrombotic 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 polymorphism in a particular gestational complication setup, and the particular life syle ( e.g., obesity, smoking ). A risk assessment strategy for women with thrombophilia and pregnancy complication has recently been presented [3].

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