NEW FRONTIERS IN COAGULATION

Thrombophilia and pregnancy

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Inherited and acquired thrombophilia are the main cause of thrombosis in pregnant women. A growing number of reports over the last years have suggested that these disorders are also associated with an increased incidence of vascular pathologies resulting in poor gestational outcome. This review covers recent data concerning thrombophilia and vascular placental pathology, and discusses available therapeutic modalities to prevent placental vascular thrombosis and maximize successful gestational outcome.

Venous thromboembolism

Pregnancy is a hypercoagulable state. Thrombophilic risk factor are found in the majority (50–70%) of women with gestational venous thromboembolism (VTE). The prevalence of VTE during gestation and puerperium is increased in women with inherited thrombophilic states such as antithrombin, protein C and protein S deficiencies [1,2]. Recent data suggest that the Factor V Leiden mutation and the Factor II G20210A allele variation (Factor II mutation) are important risk factors for VTE in pregnant women. Likewise, the Factor II mutation is 3–5 times more prevalent in gestational VTE (10–20%) than in normal Caucasian pregnancy populations (2–5%). However, most carriers of Factor V Leiden mutation or Factor II G20210A will not develop clinical symptoms during gestation [3]. Antiphospholipid antibodies can be found in 10–20% of gestational VTE cases.

The risk for a first episode of gestational venous thromboembolism (VTE) is about 1/200 and 1/300 for Factor II mutation and Factor V Leiden mutation, respectively [3]. However, the risk for recurrent gestational VTE in women who had experienced VTE in the past is about 10 to 20-fold higher and is in the range of 5% (range 2–13%) and is particularly high in women who harbor thrombophilia and where previous event was during pregnancy or hormonal therapy. In view of its high prevalence thrombophilia should be searched for in women with gestational VTE.

Recurrent fetal loss

Recurrent fetal loss (RFL) defined as three or more pregnancy loss is a well-established finding in certain acquired thrombophilic disorders, such as antiphospholipid syndrome [4] and essential thrombocytopenia [5].

A case-control study in 60 women with the inherited thrombophilias, antithrombin, protein C and protein S deficiencies documented an increased risk for RFL [6]. Of 188 pregnancies in women with thrombophilia, 42 (22%) resulted in pregnancy loss compared to 23/202 (11%) in controls: odds ratio (OR) 2.0; 95% confidence interval (CI) 1.2–3.3 [6]. 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 intranuclear fetal death [7].

A number of recent case-control studies have evaluated the prevalence of the Factor V Leiden mutation in women with RFL. Despite differences in ethnic Caucasian subpopulations and selection criteria for RFL, three studies documented signifi-
cantly increased prevalence of Factor V Leiden mutation in women with RFL.

In women with RFL of unknown cause, following exclusion of chromosomal abnormalities, infections, anatomic alterations, and endocrinologic dysfunction, studies by Grandone et al. [8] and by our group [9] have suggested that evaluation for the Factor V Leiden mutation is highly warranted since a significant percentage of women with RFL are found to be carriers of the mutation. Nevertheless, it should be emphasized that other reports did not document an association between the Factor V Leiden mutation and RFL [10]. The risk for RFL is greater in homozygous carriers than in heterozygous carriers of the Factor V Leiden mutation [11].

Of interest, activated protein C (APC) -resistance in the absence of the Factor V Leiden mutation has also been associated with pregnancy loss [12,13]. A potential explanation for the association between RFL and APC-resistance is that the APC-sensitivity ratio falls progressively throughout normal pregnancy either in correlation with changes in Factor VIII, Factor V and protein S levels [14], or without such a correlation [15].

Women with thrombophilia have an increased percentage of losses at later stages of gestation. For example, second-trimester losses or intrauterine fetal death accounted for 57 of 158 fetal losses (36%) in 37 women with thrombophilia compared to only 23/135 (17%) in women with RFL without thrombophilia \( (P=0.0004) \) [16]. Activated protein C resistance and the Factor V Leiden mutation are more common in women with second-trimester pregnancy loss [16] and in women with post-embryonic first-trimester losses [17].

Combinations of thrombophilic states may further increase the risk for RPL. For example, coexistence of the Factor V Leiden and homocysteinuria [18] or a combination of the Factor V Leiden with familial antiphospholipid syndrome [19] was reported to result in thrombosis and recurrent fetal loss. It is therefore not surprising that the European Prospective Cohort on Thrombophilia (EPCOT) study documented the highest odds ratio for stillbirth \( (OR = 14.3, \ 95\%\ CI\ 2.4\textit{--}86) \) in patients with combined thrombophilic defects [20]. In our recent study involving 76 women with RFL, 6 \( (8\%) \) had a combination of thrombophilic polymorphisms compared to 1/106 \( (0.9\%) \) of controls \( (P<0.02) \) [9]. Factor II mutation and homozygosity for the variant methylene tetrahydrofolate reductase C677T allele variation both contribute to RPL when presenting in combination with other thrombophilic defects.

**Placental vascular complications**

Pre-eclampsia affect 3--5% of all pregnancies. Whether pre-eclampsia is associated with thrombophilia is currently debatable. However, the body of evidence and meta-analysis suggest that thrombophilia and particularly Factor V Leiden, Factor II mutation and hyperhomocysteinemia are associated with severe early onset pre-eclampsia [21]. Similar debate is carried out in regard to intrauterine growth restriction (IUGR). It is suggested that thrombophilia is associated with severe but not with mild IUGR [22,23]. A small number of studies suggest an association of placental abruption with thrombophilia [21].

Without therapeutic intervention, less than 20% of gestations in women with thrombophilia and RFL result in live birth [9]. This is similar to rates reported in women with the antiphospholipid syndrome who experience RFL. Mechanisms responsible for the association of inherited thrombophilia with RFL have not been elucidated. Pathological studies of placentas obtained from gestations terminated by fetal loss have revealed thrombotic changes and infarcts. These can be observed in the maternal vessels in a large proportion of placentas of women with stillbirth [24].

**Therapeutic regimens**

Women with previous VTE who harbor thrombophilia should receive LMWH prophylaxis during gestation. Women with thrombophilia without previous thrombotic event and without placental vascular complications, are advised to receive post-partum prophylaxis. In women with severe thrombophilia such as homozygous Factor V Leiden combined thrombophilia, antenatal prophylaxis may be warranted. Up to 65% of vascular gestational abnormalities can be accounted for by genetic thrombophilias [25], the implication is to screen for these mutations in all women with vascular gestational abnormalities. Furthermore, this high prevalence of genetic thrombophilias, which is similar to the findings in women with pregnancy-related venous thromboembolism [26], and the findings of thrombotic changes in the placenta of the majority of women with thrombophilia and stillbirth [24], suggest that antithrombotic drugs may have potential therapeutic benefit in women with gestational vascular complications.

The potential advantages of low molecular weight heparin (LMWH) over unfractionated heparin are higher antithrombotic ratio (meaning less bleeding for better antithrombotic effect), longer half-life with a potential need for only one injection per day, smaller injected volume, and less heparin-induced thrombocytopenia. A recent collaborative study has demonstrated the safety of using LMWH during 486 gestations [27]. Successful outcome was reported in 83/93 gestations (89%) in women with recurrent pregnancy loss and in all 28 gestations in women with pre-eclampsia in a previous pregnancy [27].
Administration of the LMWH enoxaparin, 20 mg day\(^{-1}\), to women with primary early RPL and impaired fibrinolytic capacity resulted in normalization of impaired fibrinolysis, conception in 16/20 (80%), and successful live birth in 13/16 (81%) [28]. We have used enoxaparin (Rhone Poulenc, France) during 61 pregnancies in 50 women with thrombophilia who presented with RPL throughout gestation and for 4 weeks into the postpartum period [31]. Enoxaparin dosage was 40 mg day\(^{-1}\), except for patients with combined thrombophilia or in case of abnormal Doppler velocimetry suggesting decreased placental perfusion, where the dosage was increased to 40 mg twice daily. In the case of previous thrombosis, LMWH therapy was continued for 6 weeks after delivery. Of the 61 pregnancies, 46 (75%) resulted in live births compared to a success rate of only 20% of prior gestations without antithrombotic therapy in these 50 women [29]. These preliminary results are encouraging. However, the optimal dosage of LMWH was recently determined in the LIVE-ENOX study, a multicenter, prospective, randomized trial comparing two doses of enoxaparin, 40 mg daily and 40 mg twice daily, in women with thrombophilia and recurrent pregnancy loss [30] in order to maximize successful gestational outcome. The study found equal efficacy – 84% vs. 78% live birth respectively suggesting that the 40 mg/day dose is sufficient for women with standard risk. Women at higher risk such as combined thrombophilia may need a higher dose [30]. Whether LMWH should be used in women with thrombophilia and previous one or two fetal losses is still not widely accepted although a recent study support this notion in women with pregnancy loss after 10 weeks of gestation. Whether women with severe early onset preeclampsia should benefit by LMWH prophylaxis on subsequent pregnancy has not been formally studied. However, reports from the LIVE-ENOX trial suggest that indeed this may be the case [31].

The role of aspirin, if any, in the setting of thrombophilia and vascular gestational abnormalities remains to be confirmed. In patients with inherited thrombophilia the value of aspirin is limited [31]. In patients with antiphospholipid syndrome, aspirin is given along with LMWH. However, whether aspirin has an added benefit to heparin or LMWH alone has not been evaluated. Prospective randomized, dose-finding studies are warranted to assess the potential advantage of LMWH in women with thrombophilia and vascular gestational abnormalities.

Unresolved Issues

Role for fetal genotype?

This is controversial. While there have been reports supporting that fetal thrombophilia is important [32], there are a number of reasons suggesting 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 are 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.

Women with unexplained pregnancy loss

The panel of thrombophilia workup is constantly expanding, for example, elevated Factor VIII levels have recently been association with RFL. Where current thrombophilia evaluation is negative, the idea is that yet undiscovered thrombophilia may be implicated, since thrombotic changes can be found in women with GVC even without thrombophilia. Following preliminary experience with antithrombotic therapy in these women, a prospective randomized multicenter trial comparing enoxaparin 40 mg day\(^{-1}\) and aspirin 75 mg day\(^{-1}\) has recently been conducted in Israel, and the results should be available soon.

Future perspectives

Future research is this field will most likely focus on four aspects. First, verification of the potential associations of the various genetic thrombophilias with gestational vascular pathologies is rapidly emerging. Second, currently 30–50% of vascular gestational pathologies cannot be accounted for by thrombophilia. Whether yet unknown novel genetic or acquired thrombophilia will be found to play a role remains to be determined. Elevated Factor VIII levels, PAI-1 4G/4G polymorphism and some EPC-R polymorphisms are potential candidates [21]. Third, the pathogenetic mechanisms responsible for placental vascular pathologies in women with thrombophilia have not been fully elucidated. Furthermore, it is not known why some 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 therapeutic modalities deserves prospective clinical trials, several of which are ongoing, to improve outcome for a large population of women who experience poor gestational outcome.

References


