Maternal-fetal haemostasis: mechanisms and clinical implications

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Epidemiology and pathogenesis of pregnancy complications

Recurrent pregnancy loss (PL) and gestational vascular complications (GVC), including placental abruption (PA), preeclampsia (PE) and small-for-gestational age (SGA) pregnancies, are main gestational pathologies associated with detrimental maternal and fetal complications, affecting 5-15% of pregnant women. These complications are often closely related heterogeneous diseases, with decreased trophoblast invasion, uteroplacental underperfusion, chronic hypoxia and placental ischemia as the suggested mechanism of their development. Up to 15% of women experience one clinically recognized PL, 5% two or more PLs, and 1-2% three or more losses(1). Preeclampsia complicates 4%-10% of nulliparous pregnancies and is twofold more frequent in primigravida. The risk of recurrent preeclampsia is about 15% after one previous event, increasing to 30% after 2 consecutive PLs(2). Serum levels of soluble Flt-1 and placenta growth factor were associated with the clinical presentation of the disease(3) and reducing circulating levels of free soluble Flt-1 in women with preeclampsia could alleviate clinical signs of the syndrome(4). Placental abruption, defined as premature separation of a normally inserted placenta prior to delivery of the fetus, complicates 1% of pregnancies. PA involving more than 50% of the placenta leads to fetal death.

Hemostatic changes during normal pregnancy and GVC

Normal pregnancy is characterized by a marked increase in the procoagulant activity, manifested by an elevation of coagulation factors and prothrombin fragment 1+2, and thrombin-antithrombin complexes in the blood, which is maximal around term. In addition, there is a profound decrease in physiologic anticoagulants, including reduction in protein S activity and acquired activated protein C (APC) resistance(5). The overall fibrinolytic activity is impaired during pregnancy but returns rapidly to normal following delivery. Levels of D-dimer increase as pregnancy progresses(6).

Alterations in the hemostatic system leading to excessive uteroplacental thrombosis are thought to be an important feature at the first stage in the pathogenesis of PE, involving reduced placental perfusion due to failed vascular remodeling in early pregnancy within the placental bed. TF and free TFPI concentrations are significantly increased in maternal plasma of PE women compared with normal pregnancy(7). The TFPI to TF ratio is significantly lower in patients with PE than in normal pregnancy and there is a higher maternal plasma concentration of PAI-1 in PE compared to normal pregnancy.

Thrombophilia and fetal loss

Acquired thrombophilia is associated with fetal loss, mainly first trimester PL, and its rate is elevated in women with essential thrombocythemia (ET). However, the JAK2V617F mutational status is inconsistently related to a higher incidence of pregnancy-associated complications. Fetal loss at or beyond week 10 and recurrent consecutive embryonic losses before week 10 are part of the obstetrical definition of anti-phospholipid syndrome (APLS). Tissue factor (TF) on maternal neutrophils is critical for the pathogenesis of aPL-induced fetal loss, suggesting functional linkage between complement component C5a, TF and neutrophil activation with the latter releasing reactive oxygen species and proteolytic enzymes leading to decidual damage and fetal wastage(8).

Hereditary thrombophilias

Several reviews and meta-analyses tried to elucidate the observed discrepancies regarding the prevalence of thrombophilic risk factors and gestational vascular complications(9,10). Conclusions of the TREATS study(10) pointed toward a significant, albeit modest, increase in the relative risk. The major findings included a higher risk for a late PL in the third trimester; stronger associations with recurrent PL; a higher risk of second trimester loss than of recurrent first trimester loss for FVL and FII 20210A heterozygotes. However, the results may be hampered by differences in design and conduction of available studies. A meta-analysis of prospective cohort studies, providing a superior methodological design, demonstrated that the probability of PL in FVL women was 52% higher, but lacked power to detect increased risks in women with FII 20210A polymorphism(11).

Evidence linking hereditary thrombophilias to PLs has not been sufficiently assessed. Routine screening of pregnant women is not
recommended; however, screening of women with previous complications is a matter of debate.

**Thrombophilia and gestational vascular complications**

The evidence linking hereditary thrombophilias to GVCs is heterogeneous, lacks systematic integration of severity and cofactors, shows modest odds ratio, and is mainly sustained in placental abruption. Routine screening of pregnant women for thrombophilia cannot be recommended. Screening of previously symptomatic women will depend on conclusive therapeutic developments in women harboring thrombophilia. While the global risk of PA was found to be significant for a heterozygous FVL or a heterozygous FII 20210A polymorphism it was not reported in prospective studies. A recent analysis performed on 22 articles showed the random effects OR for FVL to be 3.4 (1.4-8.3) and the fixed-effect OR for the FII 20210A polymorphism to be 6.7 (3.2-13).

**Placental hemostasis**

Tissue factor (TF) is also essential for embryogenesis, angiogenesis, invasion and implantation. Normally, TF is not presented on cells that are in contact with blood circulation. However, the placenta is a unique organ –its surface is in direct contact with maternal circulation and trophoblast cells constitutively express high levels of TF antigen and activity. In addition, cytotrophoblast differentiation and fusion to multinucleated cells –syncytiotrophoblasts– require initiation of apoptosis and exposure of negatively charged phospholipids on their membrane surface. The procoagulant nature of placental trophoblast and decidual cells may reflect the need for immediate inhibition of hemorrhage in the placental intervillous spaces during gestation, labor and delivery.

Despite the above mentioned observations, coagulation does not normally occur across the entire villous surface. The high levels of TF are tightly regulated by a variety of physiological anticoagulants: tissue factor pathway inhibitor (TFPI), endothelial protein C receptor, thrombomodulin and annexin V which act via a variety of mechanisms.

TFPI is highly expressed in placental tissues from the 10 weeks of pregnancy up to term. TFPI is produced and pooled (50-80%) in the microvascular endothelial cells and in trophoblast cells. Placental trophoblasts obtained from GVC pregnancies have a disturbed balance between TF and TFPI. Low Molecular Weight Heparins (LMWHs) stimulate expression, synthesis and release of TFPI in endothelial cells and may exert their effect in pregnant women at risk for GVC, by modulating local hemostasis at the placental syncytiotrophoblast surface.

Heparanase cleaves heparan sulfate at specific sites, leading to a release of growth factors that may be involved in placentation and trophoblast invasion decidualization and remodeling of the maternal vasculature in humans and mice. Heparanase up-regulates TF expression and interacts with TFPI on endothelial cells, resulting in increased cell surface coagulation activity. The regulatory effect of heparanase on TFPI and TFPI-2 in trophoblasts suggests a potential involvement of heparanase in early miscarriages.

**Microparticles in normal pregnancy and GVC**

Microparticles (MPs) are shed from cell membranes upon activation or apoptosis and vary in size as well as in phospholipids and protein composition reflecting those of their cell origin. MPs are involved in thrombosis, inflammation and vascular dysfunction and therefore, may have a potential significant role in the maternal placental crosstalk.

MPs obtained from healthy pregnant women demonstrate high procoagulant activity compared to non-pregnant females. The procoagulant activity further increases in MPs of women with GVC without a change in the TF expression, but with reduction in TFPI.

Trophoblast differentiation is assumed to yield massive shedding of TF-bearing microparticles that can be detected in the circulation of healthy pregnant women and the percentage of total TF bearing MPs significantly decreases in GVC. Circulating syncytiotrophoblast MPs in maternal blood might lead to endothelial dysfunction monocytes stimulation and excessive maternal inflammatory reaction.

**Anticoagulant therapy during gestation**

A recent review of close to 2800 treated pregnancies evaluated safety and efficacy of LMWH in pregnancy and concluded that LMWH is the anticoagulant drug of choice during gestation.

**Antithrombotics for prevention of pregnancy loss**

The role of LMWH in prevention of pregnancy complications is a major debatable issue. A study by Gris and colleagues demonstrated that in women who had thrombophilia and previous one pregnancy loss after a 10-weeks gestation, enoxaparin at a dose of 40 mg daily resulted in a significantly better live birth rate compared with low dose aspirin (86% vs 29%, respectively). LIVE-ENOX is a multicenter, prospective, randomized study comparing two doses of enoxaparin, 40 mg/d and 40 mg/ever 12 h, in women with thrombophilia and a history of pregnancy loss. 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. A study comparing enoxaparin 40 mg/d to low dose aspirin, reported similar live birth rate in women with unexplained pregnancy loss in whom thrombophilia was excluded. Two recent prospective multicenter randomized trials, ALIFE and SPIN, reported that antithrombotic prophylaxis did not improve pregnancy outcome in women with at least 2 unexplained pregnancy losses. However, thrombophilia cases were a small minority in these trials and the majority of cases of unexplained pregnancy loss could be attributed to other causes, including aneuploidy.
Antithrombotics for prevention of gestational vascular complications

A Canadian randomized study compared dalteparin 5000 units/d versus no prophylaxis in 110 women without identifiable thrombophilia who had prior placental-mediated complications26.

Dalteparin was associated with a lower rate of the composite primary outcome (severe pre-eclampsia, birth weight less than the 5th percentile, major placental abruption) which occurred in 5.5% of those in the dalteparin arm compared to 23.6% in the no prophylaxis arm (OR 0.15, 95% CI 0.03-0.70, p=0.016). In a French study27, 160 women with prior objectively confirmed placental abruption were randomised to enoxaparin 4000 IU per day until 36 weeks or to no drug intervention. The primary composite outcome consisted of any of the following: pre-eclampsia, SGA placental abruption or IUFD. The primary outcome was significantly reduced from 31.3% (25/80) in the no intervention group to 12.5% (10/80) in the enoxaparin group. While promising, subsequent studies will be required to solidify these findings.

In summary, prevention of placenta-mediated complications is an unmet major health issue. Understanding of the pathophysiological and pathological placental and systemic hemostatic alterations will pave the way for prospective interventional studies.

References