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## Fetal Thrombophilia

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### 1. Introduction

Pregnancy is physiologically characterized by an increased procoagulant activity; in fact, pregnant women have two- to fivefold higher risk for venous thromboembolism compared with nonpregnant women (Grandone et al., 1998). Coagulation factors VII, X, VIII, fibrinogen, von Willebrand factor, prothrombin fragment 1 and 2, and thrombin-antithrombin complexes increase (Bremme, 2003). In parallel, there is a decrease of physiologic anticoagulants such as protein S and the acquisition of activated protein C resistance. These physiologic changes appear to relate to the development of an adequate placental perfusion and provide a protective mechanism for hemostasis during delivery. A hypercoagulable state may expose, however, the pregnant women to thrombotic risk during pregnancy and the immediate postpartum period. This risk is higher in women with multiple thrombophilic defects (Tranquilli et al., 2004). Congenital thrombophilia includes deficiency or defects of some factors such as antithrombin, protein C and S, and in the case of genetic specific mutations of one or more genes among these indicated: methylenetetrahydrofolate reductase (MTHFR C677 T), Prothrombin (FII G20210A), Factor V (FV G1691A), and Plasminogen activator inhibitor-1 (PAI-1 4G/5G). In the literature, thrombophilia has been reported as related to obstetric pathology; in particular, the association with intrauterine fetal death (IUFD), a complication that ranged from 4.9 to 10.4 babies in each 1,000, and where in the 12% to 50% of cases the cause remains unknown, has been confirmed (Martinelli et al., 2003; Kupferminc et al., 1999; Preston et al. 1996) or not confirmed (Gonen et al., 2005). Although thrombophilia is extensively studied for its implications in pregnancy complications, the role of different factors, the gestational age at which those factors may intervene, has not been completely elucidated, nor has it been given enough relevance to the weight of fetal thrombophilia in the origin of some specific form of those obstetric complications (Tranquilli et al., 2006). Most of the actual studies in the literature have focused their attention on maternal biologic samples and considering exclusively the genetic contribution of the mother.

### 2. Placental genetics and biology

The placenta is the highly specialised organ of pregnancy that supports the normal growth and development of the fetus. Changes in placental development and function have dramatic effects on the fetus and its ability to cope with the intrauterine environment. Implantation and the formation of the placenta is a highly coordinated process involving

interaction between maternal and embryonic cells. Trophoblast cell invasion of uterine tissues and remodelling of uterine spiral arterial walls ensures that the developing fetoplacental unit receives the necessary supply of blood and that efficient transfer of nutrients and gases and the removal of wastes can take place. Different types of placentation are categorised according to the number and types of layers between the maternal and fetal circulations, the human placenta is defined as a “haemochorial” villous organ. In the hemochorial placentation the wall of maternal blood vessels going towards the implantation site is breached and maternal blood bathes placental cells. In this process, maternal blood passes through channels that are lined by placental trophoblast cells (Georgiades et al., 2002). This situation contrasts with all other vascular beds where the blood vessel endothelium lies at the blood tissue interface. The human trophoblast cells express a range of gene products that are expressed normally by the endothelium and that regulate the hemostatic function. These include molecules that regulate thrombin activity (thrombomodulin, endothelial protein C receptor, tissue factor pathway inhibitor), regulators of vasodilation and platelet function (nitric oxide synthase 2, cyclooxygenase 2 and prostacyclin synthase) and some regulators of fibrinolysis (plasminogen activator inhibitor, tissue plasminogen activator). These findings suggest that, although derived from a distinct developmental lineage, trophoblast cells mimic endothelial cells in their ability to partake in anticoagulant and fibrinolytic activities. Trophoblast cells are derived from the zygote and are genetically identical to the fetus (Sood, 2009). The development of gene “knock-out” and transgenic animal models indicate that complete absence of tissue factor, tissue factor pathway inhibitor or prothrombin is lethal in the developing mouse embryo. Placental thrombi resulting in placental infarction may also occur on either side of the maternal-fetal interface and may have serious implications for the mother or her fetus, including an increased risk for perinatal morbidity and mortality (Fuke et al., 1994; Redline et al., 1995). A placental infarct is an area of placental parenchyma that has undergone ischemic necrosis; it may occur on either side of the maternal-fetal interface. Development of the fetal arterial blood supply to the placenta begins as early as 18 to 20 days after conception. The fetal placental vessels vary little from vessels of other organs and are lined by endothelial cells. Endothelium-lined vessels are dependent on the normal balance of procoagulant and anticoagulant mechanisms for damage repair and maintaining blood fluidity. Failure to maintain this delicate balance in the presence of a fetal hypercoagulable state may result in placental infarction in the distribution of fetal vessels and may even result in early spontaneous miscarriage. Furthermore placental infarction is more common in women with severe preeclampsia (Salafia et al., 1995) but it is not known whether it precedes the onset of disease or develops as a consequence. Because vascular features of the placenta seem to be involved, and because the placenta is of fetal origin, fetal genes related to vascular conditions could be relevant. In cases of maternal thrombophilia associated with fetal growth restriction (FGR), maternal floor infarction of the placenta, which is characterized by deposition of fibrinoid material, could be found not only in the maternal surface but also in intervillous spaces of the placenta (Adams-Chapman et al., 2002). Thus, both maternal thrombophilia and infarction of intervillous spaces of the placenta could be causes of fetal growth restriction. Antiphospholipid antibodies syndrome (APS) represents a singular case of maternal and fetal thrombophilia since the antiphospholipid antibodies cross the placental wall. The hypothesis that hypercoagulability of APS was in some way impacting the utero-placental circulation is supported by the finding of intervillous

thrombosis, extensive villous fibrosis, or rather marked infarction in some placentas of APS pregnancies. Numerous possible mechanisms of thrombosis in the intervillous space have been considered such as increased tissue factor (Branch et al., 1993; Dobado-Berrios et al., 1999) or prostacyclin-thromboxane pathway (Peaceman et al., 1993). If the thrombotic tendency may explain the later placental insufficiency, a particularly attractive candidate mechanism for early pregnancy loss as well as placental insufficiency in later pregnancy is aPL-mediated inhibition of trophoblast invasion (Di Simone et al., 2000).

### 3. Fetal and neonatal genetics

Despite the number of studies that have confirmed or not confirmed an association between inherited thrombophilias and pregnancy complications, it remains difficult to establish the exact risk figures for particular adverse events in the presence of genetic thrombophilic mutations. The complexity of the placental disorders of pregnancy has led more Authors to speculate that a feto-maternal genome interaction is plausible (Lie et al., 1998). When the fetus itself has an inherited risk of thrombosis, pregnancy is also more prone to placental infarction at the maternal-fetal interface resulting in an increased risk for intrauterine death as compared with fetuses from uncomplicated pregnancies. This is consistent with the observation that women who are homozygous of factor V Leiden mutation, an inherited risk for thrombosis, are even more prone to fetal loss (Meinardi et al., 1999). A higher prevalence of fetal genetic risk factors for thrombosis (factor V Leiden or prothrombin 20210A allele) was found in fetuses born from a pregnancy complicated with intrauterine fetal death as compared with the prevalence of a historic control group (Dekker et al., 2004). It has been speculated that the Factor V Leiden mutation could contribute to the development of obstetric complications by promoting the formation of microthrombi in the placenta, thus compromising fetomaternal circulation (Younis et al., 1997). By the results of Tranquilli et al. (Tranquilli et al. 2010) no higher risk was observed when a singular gene mutation occurs. On the contrary, the mutation of Factor V is significantly more frequent when an intrauterine fetal demise occurs. The results obtained by the PAI-1 and MTHFR gene analysis are particularly interesting because was observed a cumulative higher risk for intrauterine fetal demise when a double condition of homozygosity occurs relative to the two genes, according to other investigators (Alonso et al., 2002; Pickering et al., 2001). The association between homozygosity for polymorphism of MTHFR and PAI-1 with the thrombotic phenomenons is controversial, but seem to be in accord with Nelen et al. (Nelen et al., 1997), who described the double condition of homozygosity MTHFR T/T and PAI-1 4 G/4 G as a cause contributing to the pregnancy loss. The common mutation analyzed in the MTHFR gene has been reported to reduce the enzymatic activity. This variant is responsible of elevated plasmatic levels of homocysteine mainly after an oral load of methionine: the condition of homozygosity for MTHFR T/T predisposes to the onset of blood hyperhomocysteinemia (Jacques et al., 1996). PAI-1 is the main factor of the regulation of the Plasminogen activators, and homozygosity for PAI 4 G/4 G is associated with increased PAI-1 levels and decrease fibrinolytic activity, which lead to a reduction of the trophoblast's ability to invade into the endometrium and compromise the successful placentation. The underlying hypothesis is that thrombophilia mediated by the physiologic hyperestrogenemia of pregnancy may be synergistic, with a genetic thrombophilic pattern promoting thrombus formation in the spiral arteries of the placenta, placental insufficiency, and pregnancy loss (Paidas et al., 2004). Jivraj et al. (16) reported that only multiple thrombophilic mutations in either partner of recurrent miscarriage couples increased the risk of miscarriages in

subsequent pregnancies 1.9-fold. Evidence suggests that preeclampsia has a maternal genetic component. Preeclampsia is more common in mothers, daughters, and sisters of women who experience preeclampsia, suggesting a role of inherited susceptibility of preeclampsia through maternal genes (Lie et al., 1998). Men who have fathered one preeclamptic pregnancy are nearly twice as likely to father a preeclamptic pregnancy in a different woman (Lie et al., 1998). Fathers who themselves came from a preeclamptic pregnancy are also at increased risk of fathering a preeclamptic pregnancy (Esplin et al., 2001). Numerous casecontrol studies of affected and unaffected mothers indicate an association between genes expressing thrombophilia and genes expressing preeclampsia (Powers et al., 1999; van Pampus et al., 1999; Kupfermanc et al., 2000; Kim et al., 2001), but none of the 27 such studies covered in a recent review (Alfirevic et al., 2002) assessed or adjusted for possible effects of fetal alleles. In fact compared with controls, preeclamptic women from 16 studies were more heterozygous for the FVL (RR=1.6; CI=1.2 to 2.1) or homozygous for the MTHFR variant (RR=1.7; CI=1.2 to 2.3). Because mothers with variant alleles also more often have children with variant alleles, adjustment for fetal alleles could be essential for correct estimation of the effects of maternal alleles (Vefring et al., 2004). Small case series suggest concordance for preeclampsia in identical twins (Lachmeijer et al., 1998; O'Shaughnessey et al., 2000), but a large cohort study found no evidence of concordance (Thornton & Macdonald, 1999). Thus, it is clear that maternal genes alone do not determine the risk. Changing paternity, and thus changing maternal-paternal genomic expression in the fetus, is associated with an increased risk of preeclampsia (Lie et al., 1998). Kajantie et al. reported that people born after pregnancies complicated by preeclampsia are at increased risk of stroke in adult life (Kajantie et al., 2009). Fetal thrombophilia may result from low birth weight. In a retrospective analysis, von-Kries and colleagues (Von-Kries et al., 2001) stated that a higher odds ratio for birth weight in the lowest quartile was observed among children carrying prothrombotic risk factors. This conclusion was not supported by Rivard and colleagues (Infante-Rivard et al., 2002) in a large case-controlled study. The placenta, which has its own hemostatic mechanisms, is probably an important locus of pathology in perinatal arterial ischemic stroke (PAS). Association between thrombosis and infarction in the placenta and peri- and neonatal infarction, the most commonly presumed mechanism being embolization to the fetus, has been reported in literature (Adams-Chapman et al., 2002). Pregnancy itself is a prothrombotic state as shift toward prothrombotic reactions is seen in women as gestation progresses through the second and third trimesters and just after gestation (Clark et al., 2003). In cases reviewed for litigation because of cerebral palsy in the child, thrombotic lesions were the most common pathology found in the placenta (Kraus et al., 1999). In a study in a national inpatient sample (James et al., 2005) reported risk factors for pregnancy-related stroke to include postnatally identified infection (OR 25); migraine (OR 16.9); thrombophilia, including history of thrombosis and the antiphospholipid syndrome (OR 16.0); systemic lupus (OR 15.2); heart disease (OR 13.2); preeclampsia (OR 4.4); diabetes (OR 2.5); and smoking (OR 1.9). A number of reports describe acquired thrombophilias in women whose pregnancies resulted in the birth of a child with perinatal stroke (Nelson, 2007). Antiphospholipid antibodies can pass from mother to child via the placenta and can alter the placenta itself, changing its function. In one of the few studies limited to perinatal arterial ischemic stroke, Gunther and colleagues (Gunther et al., 2000) found at least 1 of the 6 examined prothrombotic risk factors in 68% of affected children and in 24% of controls. Factor V Leiden mutation, the prothrombin mutation, hyperhomocystinemia, and elevated lipoprotein (a) levels have been described with increased frequency in infants who have PAS when compared with healthy control



subjects (Hogeveen et al., 2003; Golomb, 2003) . In a cohort study from the UK of Mercuri and coll. (Mercuri et al., 2001). among 24 infants with perinatal cerebral infarction confirmed by neonatal magnetic resonance imaging, 10 (42%) had at least one prothrombotic risk factor. There are some reports on an increased incidence of thrombophilic risk factors in selective cohorts of neonates who have vascular complications, such as intraventricular hemorrhage (Pet et al., 2001), retinopathy of prematurity, and necrotizing enterocolitis. Hypercoagulability may also be associated with late neurologic sequelae (Smith et al., 1976). Necrotizing enterocolitis (NEC) is associated to hematologic abnormalities, including evidence for intravascular coagulation (Hutter et al., 1976). Nonetheless, whether thrombophilic risk factors promote the occurrence of NEC or its severity remains to be proven (Kenet et al., 2006). Furthermore, neonatal posthemorrhagic ventriculomegaly, following fetal germinal matrix-intraventricular hemorrhage (GMH-IVH) diagnosed in utero by means of NMR, was recently described in a neonate found to be heterozygous for two thrombophilic patterns, factor V Leiden and methylenetetrahydrofolate reductase mutation (Ramenghi et al., 2005). The possible pathogenesis of intraventricular hemorrhage (IVH) may be vessel occlusion triggering high-pressure bleeding. The incidence of Factor V of Leiden was increased among infants reported in two case-series with IVH and as hydrocephalus (Aronis et al., 1998); however, the occurrence of periventricular leukomalacia (PVL) in patients who had IVH was not increased among FVL-heterozygous patients (Aronis et al., 1998). In a series of 29 cases Redline and Pappin demonstrated that neonatal death, intrauterine growth restriction, birth asphyxia, major thrombotic events and thrombocytopenia were the major neonatal complications associated with avascular villi (Redline et al., 1995). Retinopathy of prematurity (ROP) is considered as a multifactorial disease and was reported to be associated with hypoxia-induced angiogenesis. Since vasculogenesis may be influenced by the presence of thrombophilic risk factors Kenet et al. (Kenet et al., 2003) studied the incidence and severity of ROP was similar among premature infants who had thrombophilia as compared with nonthrombophilic infants of the study group. The prevalence of genetic prothrombotic markers (FVL, MTHFR, FII20210A) and plasma omocysteine levels were assayed in 166 premature and low-birth-weight infants but the prevalence of perinatal complications and the severity of diseases were similar among infants with or without thrombophilia, although the numbers of patients within any subgroup of complications was small.

#### 4. Therapy

A successful pregnancy requires the development of adequate placental circulation, thrombophilia may be hypothesised to be a risk factor for the placenta mediated pregnancy complications and anticoagulants (heparin and aspirin) may be of interest to prevent these complications. In clinical trials the effects of some of these drugs on the development of preeclampsia have already been investigated in pregnant women. Low-molecular-weight heparins, fractions of crude heparin with high bioavailability and a relatively long half-life, are produced by the enzymatic or chemical breakdown of unfractionated heparin and have been widely used during the last decade. It has been shown that they do not cross the human placenta in vivo. Two general hypotheses have been proposed to explain how heparin and aspirin attenuate miscarriage rates: The first involves prevention of aberrant coagulation, reducing placental ischemia and the second involves direct modulation of cell biology, preventing apoptosis and maintaining trophoblast proliferation (Yacobi et al., 2002). Since the aspirin cross the placental wall its effect may act also on the fetal side. In

randomized placebo-controlled studies, administration of aspirin throughout the first trimester, but not later than 16 weeks, or of LMWH starting at 10-11 weeks of gestation or even before conception, lowered the risk of developing hypertensive disorders and intrauterine growth restriction in pregnancy (Rey et al., 2009; Duley et al., 2007). The potential effect of aspirin in improving pregnancy outcomes is due to the selective inhibition of thromboxane synthesis without impairing prostacyclin synthesis. However the placenta effect of aspirin can vary between individuals because liver metabolism, adding a reason to the why aspirin may not be good for all patients. The interplay between the coagulation system and the placenta mediated pregnancy complications may not be isolated to thrombotic effects at a vascular level leading to placental insufficiency. Recent evidence demonstrates that coagulation activation may directly impact on trophoblast cell growth and differentiation at a cellular level without thrombosis at a vascular level as an intermediary. That is, coagulation activation may play a role in the development of placental insufficiency through abnormal placental development rather than placental vascular thrombosis. The anticoagulant activity of heparin is mediated by both antithrombin dependent and independent pathways, but the role of heparin as an anti-inflammatory agent has been the subject of much investigation. Inflammation is known to play a key role in pathogenesis of preeclampsia and other obstetric complications. The immunological mechanism involves the regulation of Th1/ Th2 balance, production of inflammatory cytokines and leucocyte activation. Animal models have shown that heparin disaccharides inhibit TNF  $\alpha$  production by macrophages, and hence decrease immune mediated inflammation (Tyrell et al., 1995). The anti inflammatory effect is mediated by antithrombin and a TFPI independent pathway, by inhibition of matrix degrading enzymes, proteases and also by Selectin modulation. Mello et al. reported that the absolute risk of pre-eclampsia was reduced from 28.2% (11/39) in the no drug intervention group to 7.3% (3/41) in the dalteparin group. The absolute risk of early onset preeclampsia ( $\leq 34$  weeks gestation) was similarly reduced from 20.5% (8/39) in the no drug intervention group to 2.4% (1/41) as was fetal growth restriction from 43.6% (17/39) in the no drug intervention group to 9.8% (4/41) in the dalteparin group (Mello et al., 2005). Further prospective studies are needed to assess whether inherited or acquired thrombophilia increases the risk of development and recurrence Placental mediated disorders of pregnancy. The administration of prophylactic doses of low-molecular weight heparin from the beginning of pregnancy may reduce the recurrence rate of these disorders. If the use of antithrombotic therapy will be proven to be effective in reducing maternal and perinatal morbidity and mortality, acceptable, and cost effective, then a screening program should be planned to identify women and fetus with thrombophilia and a past history of severe complications of pregnancy.

## 5. Conclusions

Inherited and acquired factors may determine thrombophilia. Given that some complications of pregnancy are not always associated with maternal thrombophilia, controversy still exists on the exact impact of the disorders with the adverse pregnancy outcomes. While we are convinced that thrombophilias are extensively implicated in pregnancy complications, we feel that there has not been completely elucidated the role of the different factors, the gestational age at which those factors may intervene, nor has been given enough relevance to the weight of fetal thrombophilias in the origin of some specific form of those obstetric complications. The homozygosity of polymorphism in placental tissue necessarily includes a role of the father's genetic pattern in pregnancy destiny, and

may identify a “fetal thrombophilic status” inherited from both parents. Maternal thrombophilias may be responsible for venous thromboembolism, preeclampsia HELLP syndrome and eclampsia, whereas fetal thrombophilia, may account for fetal growth restriction or stillbirth. This last would also explain some stillbirth or repeated late miscarriage observed in non-thrombophilic mothers. The two sides of thrombophilia may, of course, concur, resulting in the more severe clinical presentations. The clinical implications of these hypothesis need to be addressed in future research to answer the question of whether or not maternal/paternal/fetal thrombophilia should be treated with low molecular-weight heparin and/or low dose aspirin.

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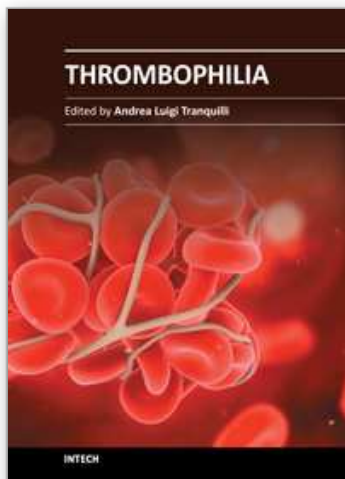
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## **Thrombophilia**

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Thrombophilia(s) is a condition of increased tendency to form blood clots. This condition may be inherited or acquired, and this is why the term is often used in plural. People who have thrombophilia are at greater risk of having thromboembolic complications, such as deep venous thrombosis, pulmonary embolism or cardiovascular complications, like stroke or myocardial infarction, nevertheless those complications are rare and it is possible that those individuals will never encounter clotting problems in their whole life. The enhanced blood coagulability is exacerbated under conditions of prolonged immobility, surgical interventions and most of all during pregnancy and puerperium, and the use of estrogen contraception. This is the reason why many obstetricians-gynecologists became involved in this field aside the hematologists: women are more frequently at risk. The availability of new lab tests for hereditary thrombophilia(s) has opened a new era with reflections on epidemiology, primary healthcare, prevention and prophylaxis, so that thrombophilia is one of the hottest topics in contemporary medicine.

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