The microangiopathy of pregnancy

Hypercoagulability occurs in uncomplicated pregnancies, beginning already during the first trimester of gestation. Fibrinogen and factor VIII levels show a progressive increase, accompanied during the second trimester by an increase in VWF levels, while factor XIII levels progressively decrease to 50% during the third trimester. This is consistent with increased in vivo thrombin generation and fibrin formation, leading to an increased antithrombotic state. During pregnancy a condition of acquired protein C resistance is relatively common, due to the increase in factor VIII and V levels and, more important, to their increased state of activation. Global fibrinolytic activity is depressed until delivery, mainly due to increased levels of plasminogen activator inhibitors 1 and 2. Moderate thrombocytopenia occurs during the last stages of pregnancy and is mainly due to hemodilution.

Preeclampsia represents the most common manifestation of pregnancy-associated microangiopathy and has still undefined etiology. A defect of placentation is now considered a major risk factor for preeclampsia: The physiologic growth of the extravillous trophoblast is biphasic. The first wave of growth (12th week of gestation) affects the intradecidual portion of the spiral arteries; the second wave (14–16th week) affects the intramembranous portion of the same arterioles. In uncomplicated pregnancies, spiral arteries undergo morphological modifications with partial substitution of a fibrin-rich matrix for elastic lamina and adventitia smooth muscle cells. These modifications allow for greater capacity and reduced resistance to blood flow. In preeclampsia, only the first wave occurs effectively, leading to necrosis of the syncitiotrophoblast, active proliferation of the cytotoxiphoblast and vasocostriction of the fetal placental circulation, eventually resulting in obliterator endarteritis. The presence of chorial villi, but not necessarily of the fetus, is an absolute prerequisite for the development of preeclampsia, which occurs more frequently whenever they are highly represented (mola, twins, fetal hydrops). Preeclampsia is associated with vasospasm, endothelial damage and activation of the coagulation pathway and is recognized in 3% to 5% of pregnancies. The disease involves a maternal and a fetal syndrome. Maternal complications include thrombocytopenia, disseminated intravascular coagulation, HELLP syndrome and may lead to kidney, liver and respiratory failure. Fetal complications are represented by intrauterine growth retardation, possibly resulting in perinatal mortality or severe morbidity, including proliferative retinopathy, intraventricular hemorrhage, necrotic enterocolitis or leukomalacia.

Preeclampsia rates among the more common causes of maternal mortality in developed countries. Hypertension-induced cerebral hemorrhage was used to be the most common preeclampsia-induced cause of maternal death. With the introduction of effective anti-hypertensive drugs, acute liver failure and acute respiratory distress syndrome, both characterized by neutrophil infiltration, are now more commonly encountered. The maternal syndrome of preeclampsia is associated with a prothrombotic state, exacerbating physiological hypercoagulability. Fibrinogen, von Willebrand factor and FVIII levels increase earlier and to a greater extent in preeclampsia. Accordingly, PAI-1 levels are also increased, reflecting endothelial sufficiency. Increased proteolysis of endothelial membrane receptors is reflected by the increase in soluble thrombomodulin levels, which may be predictive of future development of preeclampsia already during the second trimester of pregnancy. Chromosomal translocations, anatomical uterine abnormalities, autoimmune or endocrine disease may favor thrombosis of placental vessels, but they are recognized in a minority of instances. On the other hand, thrombophilic
Table 1. Relationship between gestational age at onset of preeclampsia and perinatal outcome at the S. Raffaele Hospital, years 1990-1997.

<table>
<thead>
<tr>
<th>Gestational week at onset of preeclampsia</th>
<th>No.</th>
<th>Fetal-neonatal mortality %</th>
<th>Severe neonatal morbidity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>34</td>
<td>35.3</td>
<td>32.4</td>
</tr>
<tr>
<td>28-29</td>
<td>30</td>
<td>13.3</td>
<td>36.7</td>
</tr>
<tr>
<td>30-33</td>
<td>141</td>
<td>7.1</td>
<td>9.9</td>
</tr>
<tr>
<td>&gt;33</td>
<td>231</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

states are not only involved in the occurrence of thromboembolism during pregnancy, but may be relevant in the occurrence of other complications of pregnancy, like preeclampsia. After the milestone study of Kupferminc et al., a number of reports have investigated the association of inherited thrombophilia with preeclampsia/eclampsia. In a systematic review of 18 studies published in 2002, women with preeclampsia/eclampsia were more likely to be carriers of heterozygous factor V Leiden mutation (OR = 1.6), heterozygous prothrombin gene G20210A mutation (OR = 2.4) and MTHFR thermolability (OR = 1.7) compared with controls (14). Protein C deficiency (OR = 21.5), protein S deficiency (OR = 12.7) and APC resistance (OR = 4.6) were also more common in women with preeclampsia/eclampsia compared with controls, but a statistically significant heterogeneity was found for most thrombophilias. In a large retrospective population based study of 404 women who developed preeclampsia or gestational hypertension also published in 2002, a number of prothrombotic gene polymorphisms inclusive of the factor V Leiden, prothrombin and MTHFR mutations did not show a different frequency compared to controls. However, a higher frequency of factor V Leiden (OR = 2.84) and of MTHFR thermolability (OR = 1.5) were observed in women with severe preeclampsia compared to controls. A yet unpublished large Italian multicentre study found an increased frequency of antiphospholipid syndrome (OR = 1.9) and of inherited thrombophilia defects (FV Leiden, prothrombin mutation, antithrombin, protein C and protein S deficiencies, hyperhomocysteinemia, OR = 2.7) in 808 women with preeclampsia compared to 808 controls. Interestingly, the increased prevalence of defects was almost exclusively limited to women with severe preeclampsia, representing about 50% of the entire patient population. The maternal syndrome of preeclampsia is also characterized by a proinflammatory state. It has been suggested that normal pregnancy is associated with an inflammatory response resulting from apoptotic placental debris entering the maternal circulation, and preeclampsia represents an extreme form of this systemic inflammatory response (SIRS). The comparison between preeclampsia and SIRS may seem counterintuitive because preeclampsia is considered to be a hypertensive state with low maternal mortality and SIRS a hypotensive state with high mortality. However, 21% of women have no documented hypertension before their first eclamptic seizure, and early onset preeclampsia is associated with a 1% risk of maternal mortality. Similarly, in SIRS, 96% of patients do not require positive inotropic support, and in the absence of superimposed sepsis, mortality is 7%. Delivery is the treatment of choice for preeclampsia. However, a conservative approach aimed at the prolongation of pregnancy, as long as foetal and maternal symptoms and signs permit, is justified in early-onset preeclampsia (<30th week of gestation) as an attempt to improve foetal prognosis. Foetal and neonatal mortality after the 30th week of gestation is less than 10%, but it increases to 30% before the 30th week of gestation. Gestational age and birth weight are independent predictors of perinatal outcome, with intact survival related to a specific birth weight for each completed week of gestation. In an Italian study of 634 neonates, intra-hospital mortality was 33% for neonates weighing less than 1500 g and 65% for those weighing less than 1000 g, with a high incidence of perinatal neurological morbidity in the latter neonates. The relationship between gestational age at onset of preeclampsia and perinatal outcome in consecutive women with preeclampsia admitted to the S. Raffaele hospital over the years 1990-1997 is reported in Table 1.

The combined outcome of foetal–neonatal mortality and neonatal morbidity was 59.4% for preeclampsia occurring before the 30th week of gestation as compared to 7.5% for preeclampsia occurring after the 30th week of gestation. In addition, there was also a clear association between birth weight and the combined outcome in this series (3.7% for birth weights ≥2000 g versus 55.4% for birth weights <1000 g).

The division of preeclampsia samples into early-onset and late-onset groups seems to discriminate between those women whose disease is more homogeneous and clinically significant (early onset preeclampsia) and those whose disease is of far lower risk and may be a physiologic variant (late-onset preeclampsia). Evolutionary advantages toward the
development of preeclampsia for the majority of cases that are mild and occur at term have been suggested. The evidence for endothelial dysfunction in preeclampsia has led to therapeutic approaches involving administration of low dose-aspirin, platelet lipoprotein IIb-IIIa antagonists, L-arginine and nitro derivatives, ketanserin or antioxidants such as vitamin C and E. Such treatments appear promising in preventing the occurrence of preeclampsia in high-risk women, but appear to have little if any value after the development of preeclampsia. In the latter condition also heparin administration has not proven beneficial. In the absence of a sensitive and specific predictive test for severe early-onset preeclampsia, with the potential exception of soluble thrombomodulin levels, what may be required is an effective disease-modifying therapy. Dexamethasone has been used with promising results in a small randomised controlled trial of women with HELLP syndrome, resulting in a 30 hours prolongation of pregnancy. Antithrombin is a natural anticoagulant, which at supra-normal concentrations may also exert anti-inflammatory activity, through an increased release of prostacyclin and the inhibition of white blood cells activation. The anti-inflammatory properties of antithrombin recognize binding to endothelial or white blood cells glycosaminoglycans as an absolute prerequisite (see ref. 28 for a review). The apparent half-life of antithrombin is reduced from 29.4 hours in normal pregnancy to 8.5 hours in preeclampsia. In a randomised, double-blind, placebo controlled study, the administration of high doses of antithrombin concentrate for one week resulted in a significant 6.6 days prolongation of pregnancy in women with severe preeclampsia (24 to 34 weeks of gestation) and in an increased birth weight. More recently, a small randomised trial in 23 preeclamptic women (24–33 weeks of gestation) has shown that the infusion of high doses of antithrombin concentrate for 5 days was associated with prolongation a 2.5 days prolongation of pregnancy and in less clinical significant bleeding compared to the infusion of the same concentrate at doses aimed to maintain circulating antithrombin levels above 80%. Although encouraging, these studies have not enough quality-controlled data to support the introduction of antithrombin supplementation in regular clinical practice. A double bind, randomised, placebo-controlled study is currently underway in 15 Italian centres evaluating the administration of an antithrombin concentrate (Kedrion S.p.A, Italy) at high doses for 7 days in patients with early-onset (<30 week of gestation) preeclampsia (Early Preeclampsia Antithrombin Study, ATIII–EPAS). The main objective of the study is the reduction in the combined endpoints of foetal-neonatal mortality and morbidity with a sample size powered to detect a 30% difference between the placebo and the active treatment arm. The results of this study should permit a better understanding of the therapeutic role of antithrombin supplementation in preeclampsia.

References
25. Dekker GA, van Geijn HP. Endothelial dys-
26. Howie PW, Prentice CR, Forbes CD. Fail-
ure of heparin therapy to affect the clin-
ical course of severe pre-eclampsia.
thrombin therapy for severe preeclamp-
sia: results of a double-blind, ran-
30. Paternoster DM, Fantinato S, Manganel-
ili F, Milani M, Nicolini U, Girolami A. Effi-
cacy of AT in pre-eclampsia: a case-con-