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Disseminated intravascular coagulation (DIC) in pregnancy and the peri-partum period

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Disseminated intravascular coagulation (DIC) is a condition characterized by a systemic activation of coagulation that leads to fibrin deposition without specific localization and occurring intravascularly. There is ample experimental and pathological evidence that the fibrin deposition in DIC contributes to multiple organ failure. The massive and ongoing activation of coagulation, may result in depletion of platelets and coagulation factors, which may cause bleeding (consumption coagulopathy).

(Pre-)eclampsia is the most common obstetrical condition associated with activation of blood coagulation resulting in macroscopical fibrin deposits in various organs in severe cases. Thrombocytopenia is an early indicator of DIC developing in the course of the HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), which complicates pregnancy induced hypertension in 5–10%, and pre-eclampsia in up to 50% of cases. The central pathophysiological stimulus of DIC in this syndrome appears to be microangiopathic hemolytic anemia (MHA) accompanying vascular endothelial damage, and platelet adhesion and activation, facilitating fibrin formation.

A more classical form of DIC may be caused by various underlying disorders, of which sepsis, trauma and malignancy are prominent, but also including a number of peri-partum haemostatic emergencies. The frequency by which peri-partum haemostatic emergencies result in DIC is dependent on the characteristics of the center. In Western hospitals, it is estimated that 1–5% of patients with DIC have a peri-partum haemostatic emergency as underlying cause. In developing countries this frequency is thought to be much higher. Peri-partum haemostatic

emergencies known to be associated with DIC are for example abruptio placenta and retained dead fetus syndrome.

Recent knowledge on important pathogenetic mechanisms that may lead to DIC-associated coagulopathy and microvascular dysfunction has resulted in novel preventive and therapeutic approaches to patients with DIC. The trigger for the activation of the coagulation system is mediated by several pro-inflammatory cytokines, expressed and released by mononuclear cells and endothelial cells. Thrombin generation proceeds via the (extrinsic) tissue factor/factor VIIa route and simultaneously occurring depression of inhibitory mechanisms, such as antithrombin III and the protein C and S system. Also, impaired fibrin degradation, due to high circulating levels of PAI-1, contributes to enhanced intravascular fibrin deposition. Interestingly, the placenta is a rich source of tissue factor and hypothetically the release of tissue factor from placental tissue in the case of abruptio placenta may be a logical pathogenetic pathway.

The diagnosis of DIC can be made by sensitive laboratory tests, however, most of these tests are not readily available in a routine setting. A reliable diagnosis can also be made on the basis of a small series of routine lab tests that can be combined in a scoring algorithm (ISTH-DIC score). Prospective validation of this score, also in patients with pregnancy and in the peri-partum period, shows promising results.

Based on the knowledge of the pathogenesis of microvascular failure and coagulation activation in DIC, strategies aimed at the inhibition of coagulation activation were developed and have been found favorable in experimental and clinical studies. In particular, restoring the function of

dysfunctional anticoagulant systems is interesting in this respect. DIC in pregnancy is characterized by a vast depletion of antithrombin and administration of antithrombin concentrate is an interesting though not very well studied option. Restoring the function of the protein C system by administration of activated protein C, was shown to be of benefit in patients with sepsis and organ failure. Patients in the pivotal prowess trial of activated protein C in sepsis were retrospectively evaluated for the presence of DIC according to the ISTH-DIC score. At baseline, 29% (454/1568) of patients had overt DIC. Overt DIC was a strong predictor of mortality, independent of APACHE II score and age. Placebo-treated patients with overt DIC had higher mortality than patients without (43% vs. 27%). Activated protein C-treated patients with overt DIC had a greater relative risk reduction in mortality than patients without (29% vs. 18%, $P=0.261$). Also the administration of activated protein C has not yet been systematically studied in pregnancy and peri-partum DIC.

The cornerstone of the management of DIC is the specific and vigorous treatment of the underlying disorder. Strategies aimed at the inhibition of coagulation activation may theoretically be justified and have been found beneficial in experimental and initial clinical studies. These strategies comprise inhibition of tissue factor-mediated activation of coagulation or restora-

tion of physiological anticoagulant pathways, by means of the administration of antithrombin concentrate, (activated) protein C, or strategies involving (recombinant) thrombomodulin.

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