OBSTETRICS

Disseminated intravascular coagulation in pregnancy: insights in pathophysiology, diagnosis and management

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Disseminated intravascular coagulation (DIC) is a life-threatening situation that can arise from a variety of obstetrical and nonobstetrical causes. Obstetrical DIC has been associated with a series of pregnancy complications including the following: (1) acute peripartum hemorrhage (uterine atony, cervical and vaginal lacerations, and uterine rupture); (2) placental abruption; (3) preeclampsia/eclampsia/hemolysis, elevated liver enzymes, and low platelet count syndrome; (4) retained stillbirth; (5) septic abortion and intrauterine infection; (6) amniotic fluid embolism; and (7) acute fatty liver of pregnancy. Prompt diagnosis and understanding of the underlying mechanisms of disease leading to this complication in essential for a favorable outcome. In recent years, novel diagnostic scores and treatment modalities along with bedside point-of-care tests were developed and may assist the clinician in the diagnosis and management of DIC. Team work and prompt treatment are essential for the successful management of patients with DIC.

Key words: acute fatty liver of pregnancy, endothelial dysfunction, hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, hemorrhage, score, trophoblast

Uncontrolled peripartum bleeding, resulting in disseminated intravascular coagulation (DIC), is one of the leading causes for maternal mortality worldwide.[1] This is in spite of an adaptive physiological mechanism that generates a physiological prothrombotic state during gestation[2,3] and the advanced medical and surgical hemostatic capabilities that have evolved during the past decades for controlling acute obstetrical blood loss.

The rate of DIC during pregnancy differ among cohorts and range from 0.03%[4] to 0.35%.[5] A series of pregnancy complications have been associated with DIC including the following: (1) acute peripartum hemorrhage (uterine atony, cervical and vaginal lacerations, and uterine rupture); (2) placental abruption; (3) preeclampsia/eclampsia/hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; (4) retained stillbirth; (5) septic abortion and intrauterine infection; (6) amniotic fluid embolism; and (7) acute fatty liver of pregnancy.[1,6]

The proportion of each disorder varies among the different reports. In a cohort[5] including 24,693 pregnancies, among those who developed DIC, 49.4% had placental abruption, 29.9% postpartum hemorrhage (PPH), 12.6% severe preeclampsia, and 5.7% a uterine rupture, whereas in a different cohort including 151,678 deliveries, the proportion of these complications in those who had DIC was placental abruption (37%), postpartum hemorrhage or hypovolemia (29%), preeclampsia/HELLP syndrome (14%), acute fatty liver (8%), sepsis (6%), and amniotic fluid embolism (6%).[4]

In most of these pregnancy complications, DIC is associated with adverse maternal outcome including massive blood products transfusion, hysterectomy, and even maternal death.[7] Therefore, prompt diagnosis and treatment are needed to reduce the morbidity and mortality that is associated with DIC.

In this review, we aim to discuss the following: (1) the pathophysiology of DIC focusing on the triad represented by exaggerated activation of coagulation, consumption of coagulopathy, and impaired synthesis coagulation as well as anticoagulation proteins; (2) the diagnosis of DIC with special attention to the available scores adding prognostic value to the laboratory parameters in patients with this dangerous condition or are at risk for its development; and (3) the principles of the treatment of DIC (the latter is discussed extensively in the literature).[6,8-17]

What is disseminated intravascular coagulation?

DIC represents a life-threatening condition that is the endpoint of uncontrolled systemic activation of the hemostatic system, leading to a simultaneous widespread microvascular thrombosis, that can compromise the blood supply to different organs and may lead to organ failure.[18] This process is associated with increased degradation of coagulation factors as well as anticoagulation proteins and followed by their impaired synthesis, leading to uncontrolled bleeding.

Acute, severe DIC is characterized by diffuse multiorgan bleeding, hemorrhagic

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Received Jan. 20, 2015; revised March 26, 2015; accepted March 29, 2015.

The authors report no conflict of interest.

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0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2015.03.054

necrosis, microthrombi in small blood vessels, and thrombi in medium and large blood vessels.[12] This condition may occur in the setting of sepsis, major trauma, and obstetric calamities. The final scenario is represented by the exhaustion of coagulation/anticoagulation factors and platelets, leading to profuse uncontrollable bleeding and often death.

In contrast to the acutely ill patient with complicated severe DIC, other patients may have mild or protracted clinical manifestations of consumption or even subclinical disease manifested by only laboratory abnormalities.[19] The clinical picture of subacute to chronic DIC is exemplified by the chronic hypercoagulability that may accompany malignancy, in particular with mucin-producing adenocarcinomas and acute promyelocytic leukemia. However, currently there are no reports in the literature regarding the occurrence of mild subacute DIC in pregnant women.

The development of DIC as a result of predisposing conditions can be a life-threatening complication and is considered one of the leading causes for maternal morbidity and mortality worldwide.[7] However, it is important to emphasize that DIC is not a disease by itself; it is always secondary to an underlying disorder that causes the uncontrolled activation of coagulation.

What are the mechanisms leading to DIC during pregnancy?

The development of DIC during pregnancy can be either abrupt as in acute abruption or PPH or continuous as can be observed in a retained dead fetus. Of interest, obstetric complications such as placental abruption, amniotic fluid embolism, and acute fatty liver of pregnancy are associated with severe early-onset DIC that is accompanied by maternal coagulopathy. The DIC in obstetric hemorrhage activates coagulation and triggers fibrinolysis. Activation of fibrinolysis leads to the production of D-dimers and fibrin-degradation products. These will interfere with platelet function and can impair myometrial contractility.[20]

Clinical presentation of DIC may be the results of the following mechanisms.

Endothelial dysfunction and platelet activation

Intact, dysfunctional, or activated cells, as well as remnants of cell surfaces, inflammatory mediators, and coagulation proteins are all part of an interplay in which uncontrolled activation of coagulation cascade leads to DIC.[21]

Endothelial cells, platelets, but in some cases also leucocytes and cancer cells can participate in the genesis of the process leading to DIC by releasing proinflammatory cytokines, propagating the activation of coagulation on their surface or inducing tissue factor (TF) expression on their membrane.[10,22-28] A systemic inflammatory response that is associated with markedly increased circulating proinflammatory cytokines such as tumor necrosis factor-α, interleukin-1 (IL-1), and interleukin-6 (IL-6) can lead to exaggerated expression of TF by leukocyte and endothelial cells.[24] This will generate an uncontrolled coagulation response that will eventually deteriorate into DIC. Lastly, the initiation of coagulation leading to thrombin generation in DIC, is mediated by the TF/factor VIIa pathway, also known as the extrinsic coagulation pathway.[12]

The most significant source of TF is not completely clear in all situations. Tissue factor may be expressed not only in mononuclear cells in response to proinflammatory cytokines (mainly IL-6) but also by vascular endothelial or cancer cells.[27-29] Despite the potent initiation of coagulation by TF, the activation of coagulation cannot be propagated if the physiological anticoagulant pathways function properly. However, in DIC all major natural anticoagulant pathways (ie, antithrombin III, protein C system, and TF pathway inhibitor [TFPI]) appear to be impaired.[30]

Plasma concentrations of antithrombin III, the most important inhibitor of thrombin, are markedly reduced during DIC because of a combination of consumption,[31] degradation by elastase from activated neutrophils,[32] and impaired synthesis.[10]

A significant depression of the protein C system may further compromise an adequate regulation of activated coagulation.[33] This impaired function of the protein C system is caused by a combination of impaired protein synthesis, cytokine-mediated down-regulation of endothelial thrombomodulin, and a fall in the concentration of the free fraction of protein S (the essential cofactor of protein C), resulting in reduced activation of protein C.[33]

Lastly, there seems to be a misbalance of TFPI function in relation to the increased TF-dependent activation of coagulation.[34]

All these anticoagulant pathways are linked to the endothelium, and it is likely that endothelial cell activation and dysfunction are an important component of the imbalance between coagulation and anticoagulation systems. Of interest, experimental and clinical studies indicate that during DIC, the fibrinolytic system is largely suppressed at the time of maximal activation of coagulation.[10,11] This inhibition of fibrinolysis is caused by a sustained rise in the plasma concentrations of plasminogen activator inhibitor (PAI)-1, the principal inhibitor of the fibrinolytic system.

Activation of platelets may also accelerate fibrin formation.[35] The expression of TF in monocytes is markedly stimulated by the presence of platelets and granulocytes in a P-selectin–dependent reaction.[29] This effect may be the result of nuclear factor kappa B activation induced by binding of activated platelets to neutrophils and mononuclear cells.[36]

During pregnancy maternal leukocytes are in a higher state of activation than in nonpregnant women[37] and have characteristics akin to sepsis.[38] However, they are well controlled during pregnancy, and it has been proposed that the trophoblast plays a role in the maintenance of the balanced systemic maternal inflammation during gestation.[39] Nevertheless, in cases of sepsis caused by an infectious agent or septic abortion and at least in some of the cases of amniotic fluid embolism,[40] this equilibrium is disturbed and the mother develops DIC.

Trophoblast properties and activation of the coagulation system

During normal gestation the trophoblast has 2 hemostatic functions: (1) to allow