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Disseminated intravascular coagulation in obstetrics, pregnancy, and gynecology: Criteria for diagnosis and management

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Syndromes of disseminated intravascular coagulation in obstetrics, pregnancy and gynecology
Objective criteria for diagnosis and management

Introduction

Disseminated intravascular coagulation is a confusing syndrome, regarding diagnostic and therapeutic modalities. Confusion and controversy stem from (1) the fact that many unrelated clinical scenario may induce DIC (2) a lack of uniformity in clinical manifestations (3) confusion regarding appropriate laboratory diagnosis and (4) unclear guidelines for management with respect to specific therapeutic modalities potentially available. Recommendations for and evaluation of management becomes even more difficult because: (1) the morbidity and survival is often dependent on the specific cause of DIC and (2) few of the generally used specific modes of therapy, heparin, antithrombin concentrate, protein C concentrate, and others, have been subjected to objective prospective randomized trials, except antithrombin concentrates.

This chapter provides specific and objective guidelines and criteria for (1) the clinical diagnosis, (2) laboratory diagnosis, and (3) to provide objective systems to assess efficacy of any given specific therapeutic modality, independent of influences of the underlying (inducing) disease causing the DIC in obstetrical, pregnancy or gynecological patients.[1,2] This approach allows for objective decisions regarding diagnosis and management in particular obstetric and gynecological settings and in

Hematological Complications in Obstetrics, Pregnancy, and Gynecology, ed. R. L. Bick *et al*. Published by Cambridge University Press.

individual patients. A general review of the etiology, pathophysiology, clinical and laboratory diagnosis, and management modalities suggested for DIC in obstetrics and gynecology is provided.

Disseminated intravascular coagulation (DIC) is an intermediary mechanism of disease usually seen in association with well-defined clinical disorders.[3,4,5,6] In obstetrics, pregnancy and gynecology, those disorders include amniotic fluid embolism, placental abruption, missed abortion, retained fetus syndrome, placenta previa (occasionally), preeclampsia/eclampsia, HELLP syndrome, ovarian cancer, uterine cancer and breast cancer. Of course, as will be discussed, the obstetric and gynecologic patient may also develop DIC secondary to other medical and surgical complications not specifically unique to obstetrics, pregnancy and gynecology, for example inflammation, infection, sepsis, etc.

The pathophysiology of DIC serves as an intermediary mechanism in many disease processes, which sometimes remain organ specific. This catastrophic syndrome spans all areas of medicine and presents a broad clinical spectrum that is confusing to many. DIC was called "consumptive coagulopathy" in early literature;[7,8] this is no longer an adequate description as very little is consumed in DIC; most factors and plasma constituents are plasmin biodegraded. Terminology following this phrase was "defibrination syndrome". The modern term is disseminated intravascular coagulation; this is a beneficial descriptive pathophysiological term if one accepts the concept that "coagulation" is expressed as both hemorrhage and thrombosis.[1,3,4,5,6] Most physicians consider DIC to be a systemic hemorrhagic syndrome however, this is only because hemorrhage is obvious and often impressive. Less commonly appreciated is the formidable microvascular thrombosis and sometimes, large vessel thrombosis occurring. The hemorrhage is often simple to contend with in patients with fulminant DIC but it is the small and large vessel thrombosis, with impairment of blood flow, ischemia, and associated end-organ damage that usually leads to irreversible morbidity and mortality. Throughout this review, fulminant DIC versus "low-grade" compensated DIC and the attendant

Table 1.1 Definition of disseminated intravascular coagulation (minimal acceptable criteria).

A systemic thrombohemorrhagic disorder seen in association with well-defined clinical situations
and
Laboratory evidence of
(1) Procoagulant activation
(2) Fibrinolytic activation
(3) Inhibitor consumption and
(4) Biochemical evidence of end-organ damage or failure

differences in clinical manifestations, laboratory findings, and treatment are discussed. However, these are often pure and theoretical, clinical spectrums of a disease continuum; patients may present anywhere in this continuum and may lapse from one end of the spectrum into another. A clear definition of DIC is outlined in Table 1.1.

Historical perspectives

The first description of disseminated intravascular coagulation comes from a lecture delivered by Dr. Walter H. Seegers titled "Factors in the Control of Bleeding".[9] Major clinical extensions of this early observation were shortly reported thereafter by Dr's. Ratnoff, Pritcher, and Colopy in an article entitled "Hemorrhagic States During Pregnancy."[10,11] In this two part article, many important observations were described including recognition that the hemorrhagic syndromes of pregnancy, now called DIC, included premature separation of the placenta, amniotic fluid embolism, the presence of a dead fetus in utero and severe pre-eclampsia or overt toxemia of pregnancy. Subsequently, more reports and descriptions of disseminated intravascular coagulation began to appear and in the mid-1960's, DIC became a clinically accepted and recognized syndrome. We owe our basic understanding and appreciation of this syndrome to the astute clinical and laboratory observations of Dr. Walter H. Seegers and Dr. Oscar D. Ratnoff and their co-workers.

Etiology

DIC is usually seen in association with well-defined clinical entities.[1,2,3,4,5,6,12,13] Those clinical disorders specific for obstetrics and gynecology are found in Table 1.2. The clinical disorders common to all medical specialties, and sometimes complicating the course of an obstetrical or gynecological patient and inducing to DIC are summarized in Table 1.3.

DIC syndromes unique to pregnancy and obstetrics

Obstetrical accidents are common events leading to disseminated intravascular coagulation. Amniotic fluid embolism with DIC is the most catastrophic and common of the life threatening obstetrical accidents.[1,2,4,5,6,7]

The syndrome of amniotic fluid embolism (AFE) is manifest by the acute onset of respiratory failure, circulatory collapse, shock and the serious thrombohemorrhagic syndrome of disseminated intravascular coagulation (DIC). The first careful description of this syndrome was by Steiner and Lushbaugh in 1941;[14] in

Table 1.2 Common causes of DIC syndromes in obstetrics and gynecology.

Obstetric accidents
Amniotic fluid embolism
Placental abruption
Placenta prevea
Preeclampsia
Eclampsia
HELLP syndrome
Retained fetus syndrome
Abortion
Gynecologic malignancy
Ovarian cancer
Uterine cancer
Breast cancer
Paraneoplastic syndromes

this landmark article, these authors describe the clinical histories of 8 obstetrical patients and demonstrated that these patients formed a distinct group with a unique pathophysiologic basis for the constellation of symptoms now associated with this syndrome. These authors were also able to duplicate this syndrome in animal models and demonstrated that amniotic fluid embolism is a relatively common cause of sudden death during labor or in the immediate post-labor period. These eight patients came from 4,000 consecutive autopsies performed over a period of 15 years, representing an incidence of 0.2% of deaths in this autopsy series. In this study, it was noted that these 8 cases were among a total of 24,200 deliveries, representing an incidence of 1 in 8,000 of their obstetrical cases. When analyzing their obstetrical deaths these authors were the first to show that amniotic fluid embolism was the most common cause of maternal death in the period during labor and within the first nine hours after labor.

Etiology of AFE

The common etiologic factor in the syndrome of amniotic fluid embolism is the entrance, by various proposed mechanisms and routes, of amniotic fluid, with or without meconium, into the systemic maternal circulation followed by embolization of amniotic fluid and it's contents to the lungs; subsequently, circulatory collapse and the development of disseminated intravascular

Table 1.3 Accepted disease entities generally associated with DIC.

Fulminant DIC	Low-grade DIC
Intravascular hemolysis	Cardiovascular diseases
Hemolytic transfusion reactions	Peripheral vascular diseases
Autoimmune diseases	Autoimmune disorders
Minor hemolysis	Renal vascular disorders
Massive transfusions	Hematologic disorders
	Inflammatory disorders
Septicemia	
Gram negative (endotoxin)	
Gram positive (mucopolysaccharides)	
Viremias	
HIV	
Hepatitis	
Varicella	
Cytomegalovirus	
Metastatic malignancy	
Leukemia	
Acute promyelocytic (M-3)	
Acute myelomonocytic (M-4)	
Many others	
Burns	
Crush injuries and tissue necrosis	
Trauma	
Acute liver disease	
Obstructive jaundice	
Acute hepatic failure	
Prosthetic devices	
Leveen or denver shunts	
Aortic balloon assist devices	
Vascular disorders	

coagulation occurs almost uniformly and instantaneously.[15] The incidence has been reported to be between 1 in 8,000 and 1 and 30,000 births.[16,17] The syndrome is commonly fatal for both the mother and child.[16] The mortality for the mother is generally 60%–80% and 50% of survivors have permanent neurological sequelae.[18,19] One recent series, however, reported a 26.4% mortality.[20] Of those surviving, thrombotic stroke is a major sequelae.[18,21,22] While the finding of amniotic fluid in maternal blood is not physiological there have been instances where

Table 1.4 Amniotic fluid embolism risk factors.

Older age
Multiparity
Physiologic intense uterine contractions
Drug-induced intense uterine contractions
Cesarean section
High cervical tear
Premature placental separation
Intra-uterine fetal death
Placental abruption
Trauma to abdomen
80% of cases develop during labor
20% may develop before or after labor

amniotic fluid may enter the systemic maternal circulation without any significant manifestations of this catastrophic syndrome.[15] In 1970, it was noted that the syndrome of amniotic fluid embolism represented 10% of all maternal deaths and a study in Sweden from 1965 to 1974 demonstrated that the syndrome of amniotic fluid embolism accounted for 22% of all maternal deaths.[15,23] Asner and co-workers have described amniotic fluid embolism to account for DIC in only 1 of 6 patients with clinically obvious disseminated intravascular coagulation and in none of 35 obstetrical patients with laboratory evidence of disseminated intravascular coagulation.[24] However, it has also been noted in a combined retrospective and prospective study of disseminated intravascular coagulation taken from the records of Massachusetts General Hospital, consisting of 60 prospectively studied patients and 15 retrospectively studied patients, that not one of these patients developed DIC in association with amniotic fluid embolism.[25] However, of these 75 DIC patients, 3 were associated with various other obstetrical accidents. Thus, when assessing the etiologic "triggers" of patients with DIC as a group, amniotic fluid embolism is quite rare. The risk factors associated with development of amniotic fluid embolism (Table 1.4) consist of older age, multiparity, marked exaggeration of uterine contraction following rupture of the uterine membranes, or markedly exaggerated uterine contraction due to the use of oxytocics or other uterine stimulatory agents, cesarean section, uterine rupture, high cervical laceration, premature separation of the placenta and intra-uterine fetal death.[17,26,27] Other factors have been spontaneous rupture of the fetal membranes and blunt trauma to the abdomen.[28,29] The syndrome can, on rare occasions, occur late in pregnancy but most commonly occurs during labor in 80% of patients; in only up to 20% of patients does the syndrome occur before labor

Table 1.5 Amniotic fluid embolism: General characteristics.

1 in 8,000 to 1 in 30,000 deliveries
10% of all maternal deaths in USA
22% of all maternal deaths in Sweden
80% overall mortality
25% will die within one hour
50% with fetal death or distress before maternal symptoms

begins and before rupture of the amniotic sac.[30,31] Twenty-five percent of women die within one hour of developing this syndrome and up to 80% will die within the first nine hours.[32,33] In 10% of women the syndrome develops without warning, usually during delivery, as amniotic fluid enters the systemic maternal circulation during an apparently normal labor and delivery unassociated with pre-delivery complications.

There is generally rapid onset of signs and symptoms of pulmonary failure and circulatory collapse; in at least 50% of patients this is followed by systemic bleeding. Fifty percent of fetuses die or develop intra-uterine asphyxia/distress before the sudden maternal onset of acute respiratory failure and circulatory collapse. In one series of 30,000 deliveries described by Graeff, there were six cases of amniotic fluid embolism; two patients died and four recovered.[15] The syndrome has also been described to occur immediately post-delivery but almost always occurs during delivery. Typically, the patient is in active delivery with the amnion intact and suddenly develops respiratory failure and circulatory collapse followed by a systemic thrombohemorrhagic disorder. The cause is only partially understood but the common etiologic event is entrance into the systemic maternal circulation of amniotic fluid which then causes extensive pulmonary micro-circulatory occlusion and local pulmonary activation of the procoagulant system; in addition, there is systemic activation of the procoagulant system.[34,35] This occurs in conjunction with intense induction of pulmonary fibrinolytic activity, presumably via release of pulmonary endothelial plasminogen activator activity in the lungs.[36,37]

Since this is a life threatening and not uncommon syndrome, all clinicians involved with obstetrics and care during delivery should be familiar with the potential of this syndrome when a patient presents with the risk factors depicted in Table 1.4, and when a patient immediately preceding, during, or immediately after delivery suddenly develops respiratory distress, shock and uncontrolled bleeding. The general characteristics of amniotic fluid embolism are presented in Table 1.5.

Pathophysiology of AFE

Amniotic fluid contains much cellular material including vernix caseosa, squamous epithelial cells and debris from the fetus.[17,38] The lipid content, cellular content, fetal debris, procoagulant activity and viscosity of amniotic fluid increase with duration of pregnancy and is at a maximum at time of delivery.[15,39,40] In most incidences, the actual mechanism(s) and site of entry of amniotic fluid into the uterine and subsequently, the systemic maternal circulation remain unclear. Indeed, several investigators examining pathologic specimens of patients with amniotic fluid embolism have, in most incidences, been unable to clearly define portals of entry.[41,42] Thus, the mechanism(s) by which amniotic fluid enters the maternal circulation in general often remains undefined. However, lacerations of the membrane and placenta may be portals of entry to the maternal venous sinuses in the uterus.[15] Entrance may be via a tear in the membranes at the placental margin with compression-injection of fluid into the maternal vessels or lacerated veins in the posterior vaginal wall or the entrance of amniotic fluid into the systemic maternal circulation may occur in the face of defect in the fetal membranes if this defect is in proximity to areas of maternal venous vessels.[15] In general, the site of entry is thought to be the area of the placental insertion or the area of the lower uterus or cervix.[15] It is possible that the cervical veins which open during labor permit entry of amniotic fluid after rupture of the membranes when the fetal head obstructs the intracervical canal, therefore blocking drainage and causing retrograde (upward) hydrostatic pressure thereby injecting amniotic fluid into open cervical veins and thus allowing entrance into the systemic returning circulation.[15] It is clear that amniotic fluid may enter the maternal circulation via a rupture of the uterus or through an abnormal placental placement site or as a part of the placental abruption syndrome. If meconium accompanies the amniotic fluid, the syndrome is accompanied by more intense DIC than occurs without meconium.[43] There appears to be many possible mechanisms by which amniotic fluid may enter the uterine and subsequently the systemic maternal circulation; however, these mechanisms are rarely documented on pathologic analysis.[41,42] Figure 1.1 demonstrates a fetal squamous cell in the maternal pulmonary microcirculation. It has recently been demonstrated that the monoclonal antibody THK-2 may be a specific pathological marker for amniotic fluid embolism.[44,45] Another suggestion is that finding fetal megakaryocytes and syncytiotrophoblastic cells in the maternal pulmonary circulation by monoclonal antibodies (CD-61 – GPIIIa, Beta-HCG and Factor VIII-vW hPL antibodies) may be diagnostic.[46]

On entering the systemic maternal circulation amniotic fluid simultaneously activates the procoagulant system leading to profound disseminated intravascular coagulation, and addition, causes intense and extensive pulmonary micro-embolization via

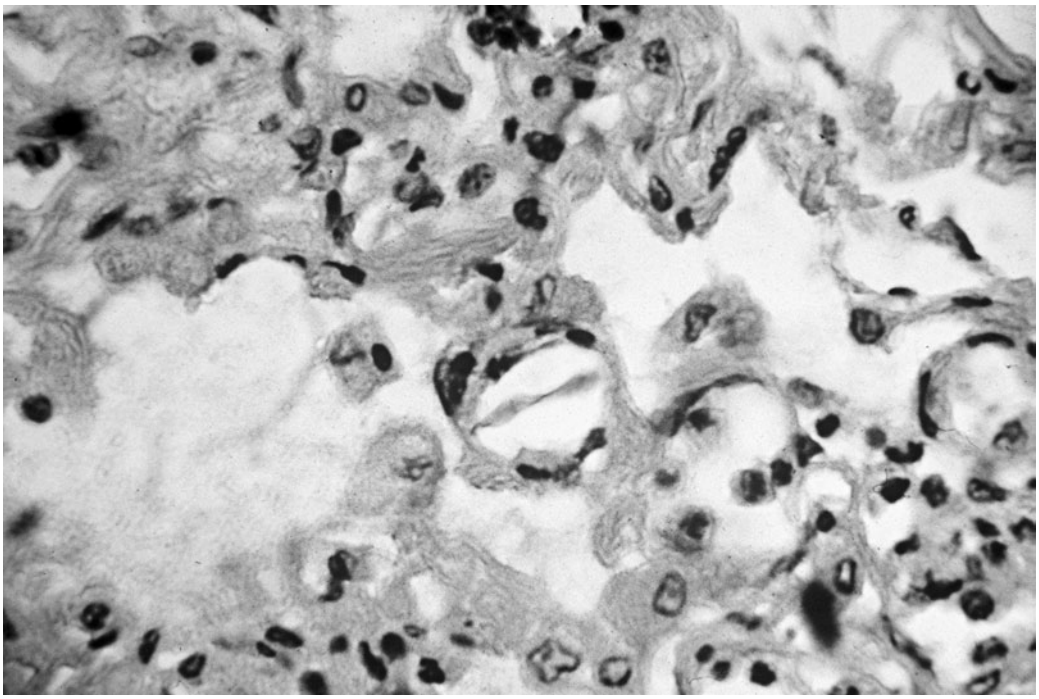

Figure 1.1 Fetal squamous cell in maternal pulmonary circulation.

not only activation of the coagulation system, but also due to hyperviscous amniotic fluid and amniotic fluid debris. As noted, this process appears more pronounced in the presence of meconium contamination.[43]

Pulmonary pathophysiology in AFE

The severity of the pulmonary manifestations are highly dependent upon the contents, amount and viscosity of amniotic fluid reaching the maternal pulmonary circulation. Of course, the higher the content of cellular elements the more viscous the material will be with cellular elements being vernix, caseosa and fetal squamous epithelial cells and complexes of squamous cellular material.[15,17] Amniotic fluid itself, as well as amniotic fluid content, will mechanically obstruct the pulmonary circulation occluding both large and small vessels with the subsequent usual manifestations of severe pulmonary embolization. This then leads to defective perfusion, defective diffusion capacity and intense vaso-constriction which, in turn, is accompanied by right heart failure and the findings of acute cor pulmonale, increased pulmonary artery pressure with subsequent decreased left ventricular

filling, decreased cardiac output and resultant tissue hypoxia and ischemia, metabolic acidosis and finally, cardiogenic shock.

Hemostasis pathophysiology in AFE

Amniotic fluid contains a highly potent total thromboplastin-like activity; this procoagulant activity increases with time of gestation.[39,40] In addition, amniotic fluid contains a relatively strong anti-fibrinolytic activity and, as such, causes a non-specific inhibition of the fibrinolytic system; this activity of amniotic fluid also increases during gestation.[24] The fibrinolytic inhibition activity may predispose a patient to DIC and diffuse thrombotic phenomenon by inhibiting or dampering the usual secondary fibrinolytic response seen in DIC patients.[1,2,34] The secondary fibrinolytic response which usually occurs in DIC is responsible for hemorrhage due to plasmin digestion of numerous clotting factors; however, this secondary fibrinolytic response also serves to help keep the circulation free of thrombi.[47] It remains controversial if amniotic fluid itself has a direct effect on the vasculature or if this is a secondary effect of procoagulant/platelet activation.[48] However, Endothelin – 1, a potent vasoconstrictor and bronchoconstrictor, appears to be released, systemically, from circulating fetal squamous cells and may intensify the severe hemodynamic alterations noted in amniotic fluid embolism.[49]

The procoagulant activity of amniotic fluid correlates very well with the lecithin/sphingomyelin (LS) ratio during gestation.[50] Amniotic fluid, in vitro, will accelerate the prothrombin time, the activated partial thromboplastin time, the Russell's Viper Venom time and will accelerating the clotting of Factor VII deficient plasma.[51] Thus, amniotic fluid not only acts as a "total thromboplastin", but acts as a substitute for "tissue phase activation". The mechanism(s) by which amniotic fluid activates the procoagulant system is by the direct activation of Factor X, in the presence of calcium ions, to Factor Xa.[52] Factor Xa is one of the most thrombogenic substances known. Factor Xa, in the presence of Factor V and additional phospholipid (including amniotic fluid and platelet surfaces) will rapidly convert prothrombin to thrombin. Once thrombin is formed, fibrinogen is converted to fibrin.[53] Thus patients with amniotic fluid embolism may develop platelet-fibrin microthrombi throughout the systemic and pulmonary circulation. This disseminated intravascular coagulation syndrome is therefore associated with micro-circulatory thrombosis, thrombo-embolism, and hemorrhage. The pathophysiology of activation in AFE is depicted in Figure 1.2. The pathophysiology of disseminated intravascular coagulation, associated with hemorrhage and thrombosis throughout the circulation is depicted in Figure 1.3.