

Disseminated Intravascular Coagulation Syndromes in Obstetrics

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Disseminated intravascular coagulation (DIC) is a syndrome that can be initiated by a myriad of medical, surgical, and obstetric disorders. Also known as consumptive coagulopathy, DIC is a common contributor to maternal morbidity and mortality and is associated with up to 25% of maternal deaths. The etiopathogenesis of DIC is complex and currently thought to be initiated by tissue factor or thromboplastin, which is released from trophoblastic or fetal tissue, or maternal decidua or endothelium. Tissue factor activates the coagulation sequence to cause fibrin clotting and its dissolution by the fibrinolysin system. The result of this process can range from mild, clinically insignificant laboratory derangements to marked coagulopathy with bleeding at sites of minimal trauma. Although clinical recognition varies by disease severity, several organizations have attempted to standardize the diagnosis through development of scoring systems. Several important—albeit not necessarily common—obstetric disorders associated with DIC include placental abruption, amniotic fluid embolism, sepsis syndrome, and acute fatty liver of pregnancy. More common disorders include severe preeclampsia, hemolysis, elevated liver enzymes, and low platelet count syndrome, and massive obstetric hemorrhage. Importantly, many of these disorders either cause or are associated with substantive obstetric hemorrhage. Treatment of DIC is centered on two principles. The first is identification and treatment of the underlying disorder. Because many women with consumptive coagulopathy also have massive hemorrhage, the second tenet of treatment is that obstetric complications such as uterine atony or lacerations must be controlled simultaneously with prompt blood and component replacement for a salutary outcome.

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Disseminated intravascular coagulation (DIC)—also known variably as consumptive coagulopathy, defibrination syndrome, and generalized intravascular coagulation—is not a disease per se, but rather a clinicopathologic syndrome that can be initiated by a myriad of underlying diseases, conditions, or disorders. Specific to the obstetric arena, some form of

consumptive coagulopathy continues to be a concern after more than a century after DeLee's description of "temporary hemophilia" that developed in women with a placental abruption or a long-dead fetus in 1901.¹ Resultant hemostatic abnormalities with amniotic fluid embolism were later described by Ratnoff and colleagues.^{2–4} Ultimately, this clinicopathologic phenomenon culminates in a systemic intravascular activation of coagulation that completely disrupts natural hemostasis.⁵ In severe cases, this ineffective balance of natural anticoagulant mechanisms can result in widespread fibrin deposition leading to multiorgan failure.

SIGNIFICANCE

The reported incidence of DIC varies because of differing definitions and diagnostic criteria. To put this condition into the context of obstetric care in the United States, Callaghan et al⁶ reviewed delivery and postpartum hospitalizations in 2-year increments over

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a decade from the Nationwide Inpatient Sample. From 1998 to 2009, they found that the prevalence of DIC had significantly increased from 9.2 to 12.5 per 10,000 delivery hospitalizations—a 35% increase. Moreover, DIC complicating postpartum hospitalizations increased 83% over the same time period—1.2–2.2 per 10,000 delivery hospitalizations. For the most recent 2-year period of 2010–2011, DIC was reported to be the second most common severe maternal morbidity indicator—32 per 10,000 delivery hospitalizations.⁷ Even more importantly, DIC was associated with nearly one fourth of maternal deaths during this study period.⁶ Even so, DIC as the sole cause of maternal death is relatively uncommon and accounts for only 0.2% of pregnancy-related deaths in this country.⁸ Put another way, DIC is rarely the cause of death alone, but it is commonly associated with conditions leading to death. In this context, DIC is one of the most important clinical conditions in terms of maternal morbidity and mortality in obstetrics.

PHYSIOLOGY AND PATHOGENESIS

During pregnancy, a substantive increase in plasma volume is concomitantly augmented by production of most procoagulants.⁹ Importantly, fibrinogen (factor I) concentration increases approximately 50% above nonpregnant values, and during late pregnancy, it ranges from approximately 375 to 620 mg/dL.¹⁰ Thus, virtually all clotting factors increase and some of these are shown in Table 1. At the same time, there is a reduction in levels of natural anticoagulants protein C and S and tissue factor pathway inhibitor-1 as well as an acquired resistance to protein C.¹¹ In addition, profibrinolysin or

plasminogen levels increase but there is also increased inhibition of fibrinolysis.⁹ As a result of all of these alterations, the net result is that pregnancy is a procoagulant state.

The literature describing the physiologic process of coagulation continues to evolve. For many years it was proposed that there was a coagulation “cascade” or “waterfall.”¹² Instead, the current theory is that coagulation is primarily initiated by tissue factor, or thromboplastin, that forms complexes with factors VII and VIIa.^{11,13} Tissue factor is an integral membrane glycoprotein that is found in highly vascularized organs such as the brain, lungs, and placenta, and it also can be expressed constitutively by certain cell types.¹⁴ In brief, the development of tissue factor FVIIa complexes ultimately generates activated factor X to initiate clotting, whereas the previously labeled “intrinsic” pathway is responsible for the amplification of this process. This main role of tissue factor FVIIa complex in coagulation is depicted in Figure 1. The end result of this coagulation process is fibrin formation, which is then counterbalanced by the fibrinolytic system—dedicated to the removal of excess fibrin. Also shown in the schematic is the fibrinolytic system with plasminogen activated by tissue factor, and this is augmented by thrombin to produce plasmin, which lyses fibrin and fibrinogen. The end result is production of fibrinogen–fibrin split products, which include D-dimers.

The initiation of DIC begins with the release of tissue factor by any number of pathologic conditions. In most cases, tissue factor is released by damaged subendothelial tissue and stimulated monocytes, which in turn provoke release of cytokines from the

Table 1. Coagulation Parameters in the Nonpregnant and Pregnant States Stratified by First, Second, and Third Trimesters¹⁰

Coagulation Parameters	Nonpregnant Adult	1st Trimester	2nd Trimester	3rd Trimester
D-dimer (micrograms/mL)	0.22–0.74	0.05–0.95	0.32–1.29	0.13–1.7
Factor (%)				
V	50–150	75–95	72–96	60–88
VII	50–150	100–146	95–153	149–211
VIII	50–150	90–210	97–312	143–353
IX	50–150	103–172	154–217	164–235
XI	50–150	80–127	82–144	65–123
XII	50–150	78–124	90–151	129–194
Fibrinogen (mg/dL)	233–496	244–510	291–538	373–619
INR	0.9–1.04	0.89–1.05	0.85–0.97	0.80–0.94
PTT, activated (sec)	26.3–39.4	24.3–38.9	24.2–38.1	24.7–35.0
Protein C, functional (%)	70–130	78–121	83–133	67–135
Protein S, functional activity (%)	65–140	57–95	42–68	16–42
tPA (ng/mL)	1.6–13	1.8–6.0	2.4–6.6	3.3–9.2
tPA inhibitor-1 (ng/mL)	4–43	16–33	36–55	67–92

INR, international normalized ratio; PTT, partial thromboplastin time; tPA, tissue plasminogen activator.



greater are considered to be compatible with overt DIC. Other than one report of acute fatty liver of pregnancy,²¹ this algorithm has not been applied specifically to other obstetric conditions that cause DIC.

Although a number of DIC scoring systems have been developed with the aim of improving outcomes,^{22–25} none has been proven more effective than assessing pertinent laboratory values in the context of the clinical situation.

OBSTETRIC CAUSES OF DISSEMINATED INTRAVASCULAR COAGULATION

One of the central features in the management of DIC is recognizing the concomitant, underlying disorder. Although intuitive, identifying these clinical conditions is paramount in correcting the underlying disorder to reconcile the coagulopathy. For this reason, we have chosen to outline seven of the most common inciting obstetric events that may result in DIC. Examples of some parameters used to assess DIC for some of these conditions are shown in Table 2.

Placental Abruptio

The reported incidence of placental abruptio varies but averages approximately 0.5% or one in 200 births.²⁶ It is a common cause of perinatal mortality and approximately 10% of third-trimester stillborn neonates are attributed to abruptio. According to the Centers for Disease Control and Prevention, placental abruptio was the direct cause of maternal mortality in 1.1% of pregnancy-related deaths in the United States from 2006 to 2010.⁸ Extensive placental abruptio causes immediate and frequently profound DIC. This is initiated by large amounts of decidual and placental-derived tissue factor that rapidly enters the

maternal circulation to activate widespread coagulation with depletion of procoagulants.¹⁷ Clotting intensity and plasma fibrinogen depletion are related to several important factors. The first of these is the amount of placental tissue involved, and thus total abruptions typically cause more intense DIC than partial ones (Table 2; Fig. 2). Specifically, one third of women with an abruptio severe enough to kill the fetus will have a plasma fibrinogen less than 150 mg/dL.²⁷ Second, a woman with a concealed abruptio—partial or complete—more likely will exhibit DIC because the intra-uterine pressure is higher than in those patients with external vaginal bleeding. The third important factor is the baseline fibrinogen level—recall that plasma fibrinogen levels are elevated substantively in late pregnancy and range from approximately 400 to 650 mg/dL.¹⁰ Thus, a woman with a fibrinogen level of 600 mg/dL might have a level of 300 mg/dL postabruptio, which signifies massive intravascular utilization of fibrinogen, but at the same time, plasma fibrinogen concentration is sufficient to maintain hemostasis. Lastly, the duration of ongoing DIC caused by an abruptio appears to be self-limited. Although the plasma fibrinogen nadir will usually be manifest by 8 hours, continuing blood loss from the implantation site will result in procoagulant deficiency if only packed red cells are transfused.²⁷

Based on the studies of placental abruptio by Pritchard and Brekken,²⁷ the mainstay of management includes immediate resuscitation of hypovolemia as discussed under “Clinical Management.” Adequate intravenous access is obtained and laboratory studies are sent to assess the degree of coagulopathy. If there is accompanying severe preeclampsia, magnesium sulfate is given for seizure prevention. The decision concerning delivery is based on gestational age and whether the fetus is dead or alive. When there is fetal death, and

Table 2. Some Parameters That Suggest Disseminated Intravascular Coagulation in Healthy Women and Women With Obstetric Disorders

Condition	n	Platelets/Microliter	Fibrinogen (mg/dL)	Fibrin Split Products (Micrograms/mL)
Normal pregnancy ³⁷	20	278,000±68,000	415±130	5±4
Placental abruptio ³⁷				
Total abruptio	23	138,000±72,000	116±87	237±129
Partial abruptio	21	194,100±85,000	289±123	54±38
Eclampsia ³⁷	65	202,000±92,000	412±75	7±8
HELLP syndrome	27	48,600±39,000	607±238	27±27
Sepsis syndrome				
Pyelonephritis	30	235,000±43,000	456±120	6±8
Clostridium	12	139,000±74,000	243±108	107±146
Acute fatty liver ²¹	51	154,000±95,000	188±24	48±13

HELLP, hemolysis, elevated liver enzymes, and low platelet count syndrome. Data are mean±1 standard deviation or standard error of mean.



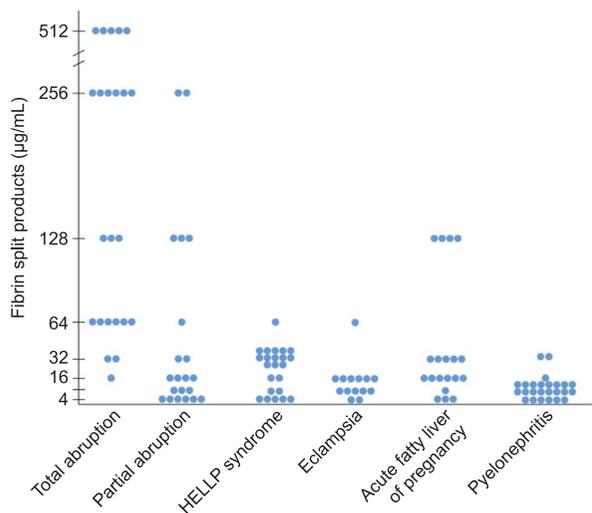


Fig. 2. Fibrin split products for varying disease-specific syndromes in obstetrics associated with disseminated intravascular coagulation. Data are from women with these various obstetric disorders studied in the Obstetrical Hematology Laboratory at Parkland Hospital from 1972 to 1995 and references 37, 46, and 61. HELLP, hemolysis, elevated liver enzymes, and low platelet count syndrome. Cunningham and Nelson. *Disseminated Intravascular Coagulopathy*. *Obstet Gynecol* 2015.

especially if there is hypofibrinogenemia, vaginal delivery is preferable. In women delivered vaginally, correction of the coagulopathy is not necessary as long as there are not any severe lacerations.^{11,27,28} If cesarean delivery becomes necessary, replacement of appropriate blood products is carried out to reverse any coagulopathy as determined by laboratory studies (see “Clinical Management”).

Amniotic Fluid Embolism

Amniotic fluid embolism can best be described as a syndrome in a woman who is actively delivering or has recently been delivered, and it is characterized by abrupt cardiovascular collapse along with variable evidence for systemic inflammatory response syndrome and DIC. Clark²⁹ recently provided a scholarly review of this process. Predisposing conditions are rapid labor; meconium-stained amniotic fluid; older maternal age; postterm pregnancy; labor induction or augmentation; eclampsia; cesarean, forceps, or vacuum delivery; placental abruption or previa; and hydramnios.^{30,31} Associated uterine hypertonus appears to be an effect rather than a cause of amniotic fluid embolism. There are varying frequencies of the syndrome reported, but when strict criteria are applied, symptomatic amniotic fluid embolism is relatively uncommon—perhaps 2 to 3 per 100,000 births.²⁹ Despite this, its high associated lethality makes it a preeminent

problem for obstetricians. Specifically, according to the Centers for Disease Control and Prevention, this syndrome caused 5.3% of pregnancy-related maternal deaths during the 5-year period ending 2010.⁸

The etiopathogenesis of amniotic fluid embolism is enigmatic. The prevailing theory is that tissue factor from amniotic fluid and fetal squames in meconium initiate the profound systemic inflammatory response syndrome and DIC. Whatever the cause, the immediate response is pulmonary and systemic hypertension followed quickly by hypotension, hypoxia, and coagulopathy. Cardiac arrest typically follows and is a common cause of death. The reported frequency of fatal cases of symptomatic amniotic fluid embolism varies, but 60% or more is a reasonable estimate average.²⁹ Survivors frequently experience adverse sequelae that include lung injury and hypoxic brain damage.

Management of amniotic fluid embolism includes immediate tracheal intubation with ventilatory assistance, cardiopulmonary resuscitation, and other supportive measures. The latter includes improved oxygenation and support of the failing myocardium along with circulatory support. Because of bleeding from operative sites or lacerations and uterine atony, there is usually need for rapid blood and component replacement as outlined under “Clinical Management.” The coagulopathy is especially problematic in women who have been or who are undergoing cesarean delivery. In undelivered women in whom cardiopulmonary resuscitation is necessary, consideration should be given for emergency cesarean delivery in an attempt to optimize these efforts. Perinatal outcomes are poor and inversely related to the maternal cardiac arrest-to-delivery interval.³⁰

PREECLAMPSIA, ECLAMPSIA, AND HEMOLYSIS, ELEVATED LIVER ENZYMES, AND LOW PLATELET COUNT SYNDROME

It was once widely held that DIC was a fundamental feature of the preeclampsia syndrome.³² This belief was stimulated by findings of thrombocytopenia and microangiopathic hemolysis as well as massive fibrin deposition found at autopsy in women with severe preeclampsia and eclampsia. It was also known at that time that some degree of hepatocellular necrosis was commonly found in women dying of eclampsia. Soon thereafter it was discovered that the serum analytes for hepatic transaminases—*aspartate* and *alanine transferase*—were directly related to the presence of hepatocellular necrosis. This led Weinstein in 1982 to coin the term HELLP syndrome—*H*=hemolysis, *EL*=elevated liver enzymes, and *LP*=low platelet count.³³ It is



generally agreed that HELLP syndrome is usually diagnosed in preeclamptic women by the triad of thrombocytopenia, elevated hepatic transaminases— aspartate transferase and alanine transferase, and microangiopathic hemolysis detected either by abnormally high lactate dehydrogenase levels or abnormally low haptoglobin levels.^{34,35} Generally speaking, sicker patients have progressively more abnormal laboratory findings. Even so, the principal differentiating factor is that the vast majority of women with preeclampsia or HELLP syndromes do not have evidence of liver dysfunction. Appreciable hepatic dysfunction characterized by low cholesterol and high bilirubin levels, low levels of fibrinogen and other procoagulants, and a prolonged prothrombin time are characteristic of acute fatty liver of pregnancy³⁶ (see “Acute Fatty Liver of Pregnancy”).

Thus, the preeclampsia syndrome includes platelet activation, dysfunction, and increased adherence along with microangiopathic hemolysis.⁹ At the same time, however, preeclampsia, eclampsia, and HELLP syndrome are usually not associated with clinically relevant DIC.^{37–39} Shown in Table 2 are mean values for platelets, fibrinogen, and fibrin split products in women with eclampsia or HELLP syndrome. Except for platelets, the values are similar to those levels measured in late normal pregnancy. The modest degree of elevation of fibrin split products is also compared with other conditions in Figure 2. The mild-to-moderately increased levels in some of these women, along with slightly elevated levels of thrombin–antithrombin complexes are indicative of some increased intravascular coagulation.^{38,40} It follows that treatment is not necessary for the mild DIC associated with preeclampsia, eclampsia, or HELLP syndrome. One exception is the occasional woman who will need platelet transfusions for troublesome bleeding resulting from thrombocytopenia and platelet dysfunction at the time of cesarean delivery. Other exceptions are women who have a concomitant placental abruption, acute fatty liver disease, or dilutional coagulopathy from major hemorrhage.

Sepsis Syndrome

The sepsis syndrome is induced by a systemic inflammatory response to bacteria or viruses or their byproducts such as endotoxins or exotoxins. CD4 T cells and leukocytes are stimulated to produce proinflammatory compounds that include tumor necrosis factor- α , several interleukins, other cytokines, proteases, oxidants, and bradykinin that result in a “cytokine storm.”⁴¹ Many other cellular reactions then follow that include stimulation of proinflammatory and anti-inflammatory compounds, procoagulant

activity, gene activation, receptor regulation, and immune suppression.⁴² At the same time, endotoxin stimulates endothelial cells to upregulate tissue factor and thus procoagulant production while it decreases the anticoagulant action of activated protein C.

The severity of the sepsis syndrome is a spectrum, and the mortality rate in nonpregnant patients is 20–35% with severe sepsis and 40–60% with septic shock.⁴³ Mabie and colleagues⁴⁴ reported a 28% mortality rate in 18 pregnant women with sepsis and shock. According to the Centers for Disease Control and Prevention, sepsis caused 4.2% of pregnancy-related deaths in the United States from 2006 to 2010.⁸ The most common cause in pregnancy is urosepsis from pyelonephritis caused by *Escherichia coli* and *Klebsiella* species.^{45–47} Fortunately, in most of these women, there is minimal evidence for activation of intravascular coagulation as shown in Table 2 and Figure 2. Rarely, the woman with obstetric sepsis will develop hypercoagulability with purpura fulminans (Fig. 3).¹⁸ There are also potent bacterial exotoxins that can cause severe sepsis syndrome—*Clostridium perfringens* toxic shock syndrome, toxin-1-producing



Fig. 3. Pregnant woman at 28 weeks of gestation with severe pyelonephritis, sepsis syndrome, and preterm labor. Within 24 hours of delivering a liveborn neonate, she developed purpura fulminans and was transferred to the burn intensive care unit. She sloughed 90% of her skin and died from dermal septicemia. Reprinted from Sheffield JS, Cunningham FG. Urinary tract infection in women. *Obstet Gynecol* 2005;106:1085–92.

Cunningham and Nelson. *Disseminated Intravascular Coagulopathy*. *Obstet Gynecol* 2015.



Staphylococcus aureus, and toxic shock-like exotoxin from group A β -hemolytic streptococci.^{48,49} These exotoxins cause rapid and extensive tissue necrosis and gangrene, especially of the postpartum or postabortal uterus, and they may cause profound cardiovascular collapse. Exotoxins are also potent inducers of DIC, and some of the effects of clostridial sepsis on platelets, fibrinogen, and fibrin split products are shown in Table 2 and Figure 2.

The pathophysiologic response to this cascade is selective vasodilation with maldistribution of blood flow. Leukocyte and platelet aggregation cause capillary plugging. Worsening endothelial injury causes profound permeability capillary leakage and interstitial fluid accumulation. Depending on the degree of injury and inflammatory response, there is a pathophysiologic and clinical continuum. The sepsis syndrome has a myriad of clinical manifestations that, at least in part, are dependent on the specific invading microorganism and its particular endo- or exotoxins. These were discussed in detail by Barton and Sibai.⁴⁶

Because of the high associated mortality rate, in 2004, a consensus effort was launched as the Surviving Sepsis Campaign.⁵⁰ The cornerstone of management is early goal-directed management and prompt recognition of serious bacterial infection and close monitoring of vital signs and urine flow. The campaign calls for three basic steps to be performed as simultaneously as possible: 1) evaluation of the sepsis source and its sequelae; 2) assessment of cardiopulmonary function; and 3) immediate management. The most important step in sepsis management is rapid infusion of 2 L and sometimes as many as 4–6 L of crystalloid fluids to restore renal perfusion in severely affected women. Simultaneously, appropriately chosen broad-spectrum antimicrobials are begun. If anemia coexists with severe sepsis, blood is given along with crystalloid to maintain the hematocrit at approximately 30%.^{43,51} The use of colloid solutions is controversial.^{52,53} With severe sepsis, damage to pulmonary capillary endothelium and alveolar epithelium causes alveolar flooding and pulmonary edema—acute respiratory distress syndrome. At the same time, determinants of the DIC syndrome may be detected by laboratory studies. Treatment is outlined under “Clinical Management.” In general, with sepsis, correction of all facets of DIC is not necessary as long as the patient is not bleeding. Because of its putative central role, there have been several agents developed to block coagulation; however, none improved outcomes.^{54,55} Because continuing sepsis may prove fatal, débridement of necrotic tissue or drainage of purulent material is crucial.⁴⁶ Some examples are uterine curettage for septic abortion, hysterectomy

for a necrotic uterus, ureteral catheterization for obstructive pyelonephritis, and débridement for necrotizing fasciitis.^{46,49}

Acute Fatty Liver of Pregnancy

Also known as acute fatty metamorphosis, acute fatty liver of pregnancy is a unique syndrome with an approximate incidence of 1 per 10,000 births. It usually develops in late pregnancy and is characterized by varying degrees of hepatic failure, acute kidney injury, and moderate-to-profound consumptive coagulopathy.^{11,21,36,39} Hepatic cytoplasm is replaced with microvesicular fat—usually triglycerides—and thus the disorder has also been termed *acute yellow atrophy*. For many years the associated coagulopathy was attributed solely to hepatic failure and diminished procoagulant production.^{56,57} Since then, however, it has convincingly been shown that there is also ongoing robust DIC as well as brisk hemolysis.^{21,39,58} Specific factors that initiate the coagulopathy are unknown but may be related to maternal acidosis from liver failure or from endothelial injury.

Clinically, acute fatty liver of pregnancy is easily confused with preeclampsia and especially HELLP syndrome. Although there are many similarities between these—hypertension, thrombocytopenia, transaminitis, and hemolysis—acute fatty liver of pregnancy is further characterized by liver dysfunction that can be profound. Also with acute fatty liver of pregnancy, there is usually moderate-to-severe acute kidney injury that is worse than that usually seen with HELLP syndrome. Shown in Table 2 are comparative mean values of some coagulation studies done in women with acute fatty liver of pregnancy, placental abruption, eclampsia, and HELLP syndrome. Of the analytes associated with obstetric coagulopathy, fibrinogen levels with acute fatty liver of pregnancy were depressed second only those seen in women with placental abruption. Importantly, half of women with acute fatty liver of pregnancy had a plasma fibrinogen less than 150 mg/dL at the time of delivery. Fibrin split products are also significantly elevated (Fig. 2). Postpartum, evidence for ongoing liver injury and prolonged dysfunction with stilted recovery comes from depressed fibrinogen levels along with increasing bilirubin levels.³⁶ Continuing DIC is characterized by International Society on Thrombosis and Haemostasis DIC scores that are persistently abnormal for several days as well as continued elevation of fibrinogen–fibrin split products.²¹

Acute fatty liver is one of the most serious coagulopathies in obstetrics. Associated maternal mortality from liver failure even with state-of-the-art care approaches 10–15%.^{36,39,59,60} Management



concerns for severely affected women are dictated by the fact that the coagulopathy can be as profound as that seen in some women with a total placental abruption. This is particularly problematic in these women with acute fatty liver of pregnancy, because their reported cesarean delivery rate with a live fetus is 80–90%.^{36,39,59,60} Because of this, many of these women require large amounts of blood and procoagulant replacement to combat hemorrhage and to achieve surgical hemostasis as described under “Clinical Management.” After delivery, and after hemostasis is secured, because of brisk ongoing hemolysis with anemia, one fourth of women with acute fatty liver of pregnancy will require continuing red cell transfusions for several days postpartum.²¹

Fetal Death and Delayed Delivery

Disseminated intravascular coagulation associated with prolonged retention of a dead fetus is unusual today because fetal demise is easily confirmed by ultrasonography, and there are highly effective methods for pregnancy termination on its discovery. The pathogenesis of this coagulopathy is thought to be mediated by the slow release of tissue factor or thromboplastin from the dead fetus and the placenta.^{61,62} Currently, the syndrome is only occasionally encountered in twin or triplet pregnancy in which there is one dead co-fetus with one or two surviving fetuses in an intact and ongoing pregnancy.^{63,64} It is also encountered in women with a missed abortion of several weeks’ duration. If the surviving fetus is delivered during this time when there is a clinical coagulopathy, treatment of the coagulopathy as described under “Clinical Management” may be necessary if cesarean delivery is undertaken or if severe lacerations are incurred.

Massive Obstetric Hemorrhage

Although listed last in order, massive obstetric hemorrhage represents one of the most commonly encountered disease-specific conditions that results in consumptive coagulopathy. Hemorrhage is a major cause of maternal morbidity and mortality.^{8,65,66} Importantly, the underlying obstetric conditions that cause DIC are also frequently associated with the potential for worsening of hemorrhage, viz, placental abruption, sepsis syndrome, amniotic fluid embolism, and acute fatty liver of pregnancy. Two of the most common causes of obstetric hemorrhage include uterine atony and genital tract lacerations either of the perineum or encountered at cesarean delivery. Given the breadth of the topic of hemorrhage, we refer to the often-cited American College of Obstetricians and

Gynecologists Practice Bulletin No. 76 for a detailed review of risk factors, battery of medical measures, and surgical techniques deployed to arrest active bleeding.⁶⁷

For the purposes of the current article, our emphasis is on two important considerations when faced with torrential obstetric hemorrhage. The first is the development of a “dilutional coagulopathy” associated with massive red blood cell transfusions without replacement of clotting factors. The second is that DIC can develop early with massive obstetric hemorrhage without other underlying causes—in fact, “pure” obstetric hemorrhage is reportedly the cause of DIC in 25–35% of observational series.^{68–70} In a recent Israeli study, in one third of 87 women with DIC, the coagulopathy was attributed to uterine atony or genital tract lacerations.²⁵ Similar observations were reported from a Canadian study.⁷¹ In these patients, blood loss is a continuum and clotting dysfunction is aggravated and perpetuated because initial blood loss is replaced with packed red blood cells and crystalloid, both essentially devoid of clotting factors. This common form of consumptive coagulopathy has been variably termed blood bank coagulopathy, exsanguination coagulopathy, dilutional coagulopathy, and washout phenomenon.^{68,72,73} It was this recognition that stimulated development of massive transfusion protocols for patients still actively bleeding.⁷³ These issues become critical features of clinical management, and as discussed subsequently, the treatment of dilutional coagulopathy and DIC in these women is the same.

CLINICAL MANAGEMENT

There are two important tenets to be considered in the clinical management of pregnant women with DIC. The first is that regardless of the underlying cause, identification and treatment of the specific underlying disorder are imperative in achieving a salutary outcome. The second is that the majority of cases of severe pregnancy-associated DIC are accompanied by massive obstetric hemorrhage. As discussed, a generalized coagulopathy can be manifest by bleeding or hypercoagulability—the former is usually in the realm of the surgeon and the latter of concern to the internist.¹⁸ For the obstetrician, it can be both. Thus, it follows that any treatment algorithm for obstetric DIC must take into consideration simultaneous and prompt replacement of blood loss in addition to treatment of the accompanying DIC and its cause. Importantly, some of the aforementioned causes of DIC have specific treatments for the underlying disorder—treatment of sepsis with drainage, débridement, and antimicrobial therapy being an obvious example. In other



instances exclusive to obstetric conditions—preeclampsia, HELLP, placental abruption, and acute fatty liver of pregnancy—treatment includes delivery. A summarized treatment algorithm for the clinical management of DIC is shown in Figure 4.

It is axiomatic that if obstetric hemorrhage—for example, from a cervical laceration—is further complicated by a disorder that causes DIC—for example, placental abruption—then blood loss will be amplified. Importantly, the clinical course of many of these women with DIC is further complicated by cesarean delivery with its attendant bleeding problems. Thus, laceration repair, uterotonic agents for uterine atony, and arrest of bleeding from operative sites is an active, if not proactive, process to effect hemostasis. Further treatment includes simultaneous assessment and management of the coagulopathy and, even more importantly, recognizing the need for blood replacement given that blood loss is often underappreciated in both severity and quantity during ongoing hemorrhage.^{26,67}

Where appropriate, women should be evaluated and managed within a suitable setting with the capacity for mobilization of available resources. Given the acuity and complexity often seen in these cases, these women require admission to an acute care unit. For those undelivered, admission to a labor and delivery unit is preferable. Postpartum recovery can be managed in either a medical or surgical intensive care unit or obstetric intensive care unit where available.⁷⁴ An operative suite may also serve as an alternative for a patient needing resuscitation given the availability of monitoring, nursing, and anesthesia as well as medical and surgical care. Regardless of location, collaboration among obstetricians, anesthesia services, intensivists,

and specialists is paramount for a multidisciplinary approach to address the many facets of care often needed in these difficult cases.

Assessment of coagulation status can be accomplished using a number of assets from the bedside to the laboratory. As mentioned, vital signs, urine output, and bioassay are critical means for estimating hypovolemia and clinical coagulation in the setting of acute hemorrhage. Commonly used studies for initial survey of coagulation include a complete blood count with platelets, fibrinogen level, fibrinogen–fibrin split products, and prothrombin time and activated partial thromboplastin time. Of note, these are all central components of the aforementioned International Society on Thrombosis and Haemostasis DIC scoring system. There have been more contemporary efforts in an attempt to provide coagulation surveys with point-of-care testing availability.⁶⁸ Briefly, thromboelastography assesses the viscoelastic properties of clot formation in real time by combining information obtained from multiple coagulation tests into a single parameter. Objective measurements determined from a thromboelastography tracing include reaction time, clot formation time, α angle (α degrees or A), and maximum amplitude.^{75,76} These are taken together to calculate values for clot formation time, rate, strength, and stability. Over the past decade numerous commercially available assays have been developed; however, there are limited data that assess the utility of thromboelastography in obstetric settings.^{77,78} Further research is needed before its widespread clinical application and use.^{68,70}

The other equally important tenet in management of obstetric DIC syndromes is ongoing treatment of bleeding abnormalities. At the outset, further treatment

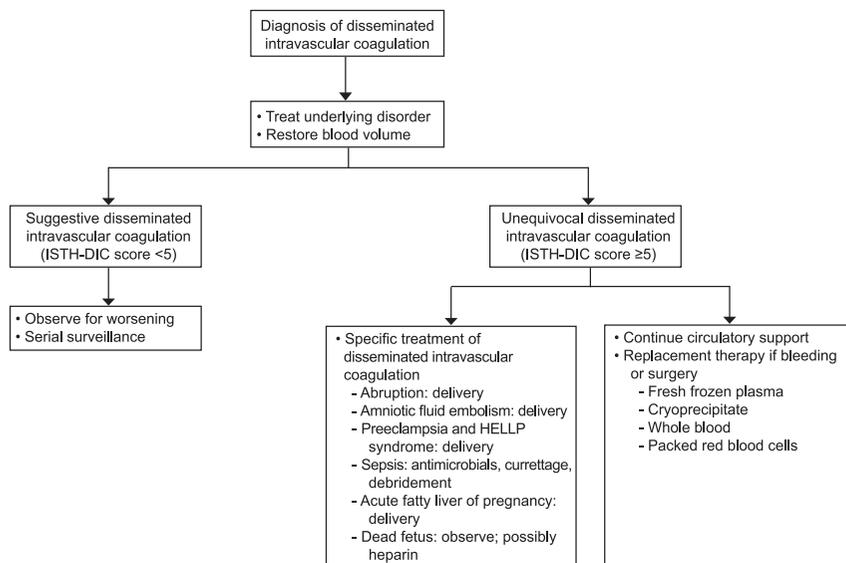


Fig. 4. Treatment algorithm for clinical management of disseminated intravascular coagulation (DIC) in obstetric syndromes. Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome and acute fatty liver of pregnancy are noted within the specific treatment considerations for DIC. ISTH, International Society on Thrombosis and Haemostasis.

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Table 3. Massive Transfusion Protocol Used at Parkland Health and Hospital System

Round	Packed RBC, 5 Units	Plasma, 3 Units	Platelets, 1 Dose	Cryoprecipitate, 1 Dose	2 mg rVIIa
1	X	X			
2	X	X	X		X
3	X	X		X	
4	X	X	X		X
5	X	X			

RBC, red blood cells; rVIIa, recombinant activated factor VII.

may not be required in women with mild coagulation abnormalities and who have no evidence of ongoing bleeding.¹⁸ To the contrary, however, in the majority of obstetric disorders, bleeding has a prominent role in clinical management. Globally, guidelines for management in women with coagulopathy and bleeding are based mainly on expert opinion that recommends replacement of red blood cells, procoagulant proteins, and platelets.¹⁸ Given that hemorrhage has such a prominent role in disease-specific conditions associated with DIC in obstetrics, basic measures for resuscitation are paramount. For example, when blood loss is excessive, a survey of indices of anemia with hematocrit is determined and physiologic monitoring for deterioration is undertaken. Urine output as a surrogate for renal blood flow is especially sensitive to changes in blood volume, and urine flow of at least 30 mL and preferably 60 mL per hour or more should be maintained as measured by an indwelling bladder catheter.²⁶ The use of colloid solutions in lieu of crystalloid is controversial, and in view of their equality, most prefer the less-expensive crystalloid.^{79,80}

After initial resuscitation, aggressive efforts for blood and component replacement are undertaken. Our preference is for whole blood for catastrophic hemorrhage and, if not available, packed red blood cells and crystalloid.^{81,82} A major drawback of the latter is depletion of platelets and clotting factors resulting in the dilutional coagulopathy, which may clinically indistinguishable from DIC with major bleeding and as discussed under “Massive Hemorrhage.” For this reason, massive transfusion protocols are typically activated when at least four to five units—and sometimes more—of red blood cells have been given to the patient who is still actively bleeding.⁷³ An example of a massive transfusion protocols is shown in Table 3 where serial rounds of components are given as needed during ongoing torrential hemorrhage. Moving forward, organizing massive transfusion protocols regimens to specific comprehensive obstetric hemorrhage protocols has been suggested to further reduce the use of blood products and improve patient safety.^{83,84} Collective appreciation for team communication, education, and

training has now resulted in simulation training entering the obstetrician’s lexicon and becoming a viable resource for training next-generation obstetricians in the management of catastrophes.^{85,86}

In addition to blood components supplied by transfusion protocols, a number of pharmacologic compounds has been used with variable success to treat DIC in nonpregnant patients. Examples include use of one of the antifibrinolytic agents—either tranexamic acid or ϵ -aminocaproic acid. At this time, use of these agents is not recommended because the fibrinolytic system is necessary for dissolution of widespread fibrin thromboses caused by generalized intravascular coagulation.¹⁸ Another example is the synthetic vitamin K-dependent protein NovoSeven—recombinant factor VIIa—which binds to exposed tissue factor at the site of injury to generate thrombin that activates platelets and coagulation. The vitamin K-dependent protein has been used to help control hemorrhage from surgery, trauma, and many other causes.⁸⁷ Most level I trauma centers include it in their massive transfusion protocols,⁸⁸ and it is included in the massive transfusion protocols used at Parkland Hospital as shown in Table 3. Recombinant factor VIIa has also been used to control severe obstetric hemorrhage.^{89,90} A principal concern raised with its use is the relatively high frequency of thromboses—both arterial and, to a lesser degree, venous thrombosis.¹¹ There is also concern regarding its effectiveness.⁸⁸ At this time, although still used for massive hemorrhage, there is insufficient clinical evidence to make firm recommendations on the obstetric use of recombinant factor VIIa for treatment of DIC.

DISCUSSION

The management of DIC in obstetrics remains a major clinical challenge. The inciting disease-specific syndrome may be complex and require directed management strategies for correction of the underlying disorders. Equally important is treatment of frequently concomitant massive blood loss that worsens the coagulopathy. With limited clinically proven management strategies available, the need for future studies is obvious. We look forward to these studies



designed to address our numerous evidence-based deficits, especially regarding management of obstetric DIC syndromes.

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