REVIEW

DIC in Pregnancy – Pathophysiology, Clinical Characteristics, Diagnostic Scores, and Treatments

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Abstract: Obstetrical hemorrhage and especially DIC (disseminated intravascular coagulation) is a leading cause for maternal mortality across the globe, often secondary to underlying maternal and/or fetal complications including placental abruption, amniotic fluid embolism, HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), retained stillbirth and acute fatty liver of pregnancy. Various obstetrical disorders can present with DIC as a complication; thus, increased awareness is key to diagnosing the condition. DIC patients can present to clinicians who may not be experienced in a variety of aspects of thrombosis and hemostasis. Hence, DIC diagnosis is often only entertained when the patient already developed uncontrollable bleeding or multi-organ failure, all of which represent unsalvageable scenarios. Beyond the clinical presentations, the main issue with DIC diagnosis is in relation to coagulation test abnormalities. It is widely believed that in DIC, patients will have prolonged prothrombin time (PT) and partial thromboplastin time (PTT), thrombocytopenia, low fibrinogen, and raised D-dimers. Diagnosis of DIC can be elusive during pregnancy and requires vigilance and knowledge of the physiologic changes during pregnancy. It can be facilitated by using a pregnancy specific DIC score including three components: 1) fibrinogen concentrations; 2) the PT difference – relating to the difference in PT result between the patient's plasma and the laboratory control; and 3) platelet count. At a cutoff of ≥26 points, the pregnancy specific DIC score has 88% sensitivity, 96% specificity, a positive likelihood ratio (LR) of 22, and a negative LR of 0.125. Management of DIC during pregnancy requires a prompt attention to the underlying condition leading to this complication, including the delivery of the patient, and correction of the hemostatic problem that can be guided by point of care testing adjusted for pregnancy.

Keywords: DIC, hyperfibrinolysis, thrombin, pregnancy specific DIC score, maternal mortality, placental abruption

Introduction

The life threatening thrombo-hemorrhagic condition known as disseminated intravascular coagulation (DIC), is generally more common in men than women apart from the reproductive years when pregnancy and its complications increase its prevalence.[1] DIC during pregnancy constitutes one of the leading causes for maternal mortality worldwide,[2,3] and its rate varies from 0.03%[4] to 0.35%.[5] This complication is often secondary to underlying maternal and/or fetal complications including placental abruption,[6–8] postpartum hemorrhage, amniotic fluid embolism, acute fatty liver of pregnancy, preeclampsia and Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome,[9] and retained stillbirth.[10] DIC is characterized by a concomitant over-activation of the coagulation and fibrinolytic

systems,[11] leading to widespread microvascular thrombosis, disruption of blood supply to different organs, ischemia, and multi-organ failure. This extensive activation of the coagulation cascade leads to consumption and depletion of platelets and coagulation proteins, which can provoke concurrent severe bleeding.[12] Of note, obstetric DIC more typically presents with bleeding complications, rather than thrombotic complications. The current review discusses the clinical characteristics, pathophysiology, diagnostic scores, and treatments of DIC in pregnancy.

DIC – Definitions and Types

The Scientific and Standardization Committee (SSC) on DIC of the International Society on Thrombosis and Haemostasis (ISTH) defined DIC as

> an acquired syndrome characterized by the intravascular activation of coagulation with a loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction.[13]

This definition highlights three important aspects: 1) it is always secondary to other causes, one of them being an obstetric related, such as abruption placentae, pre-eclampsia, or intrauterine fetal death.[14] 2) DIC represents systemic pathological activation of coagulation. Normal haemostasis refers to the formation of a thrombus in response to endothelial damage and, in these cases, the clotting and fibrinolytic processes are limited to the site of endothelial injury.[15] However, in DIC, there is uncontrolled dissemination of this localised thrombotic process which is clearly pathological. In obstetrical DIC, there is extraplacental dissemination of the activated coagulation system which is usually localised to the placenta.[16] 3) The third crucial aspect of the DIC definition is the role of microvasculature. DIC is a process which originates in the microvasculature, or the vascular endothelium, the most ubiquitous organ in the human body. Excessive and dysregulated thrombin generation due to (and causing) marked endothelial dysfunction can result in organ damage from microthrombi.[17] If microvascular dysfunction led to organ damage, it would be considered DIC according to the ISTH definition. If in obstetrical disorders, microthrombi can lead to kidney impairment or cerebrovascular ischaemia, this would be considered as a manifestation of DIC. Microthrombi in the placental vessels can be one of the pathophysiological processes which lead to the complications associated with pre-eclampsia including foetal

growth retardation and organ impairment. The microthrombi can arise from localised coagulation activation with platelet aggregation being a significant contributory factor. Most inflammatory disorders like pre-eclampsia are associated with the release of large amounts of Von Willebrand factor into the circulation. In normal circumstances, the ultra large multimer forms of the Von Willebrand factor is cleaved by a metalloprotease enzyme, ADAMTS-13. But in severe inflammation, the enzyme is quenched by the inordinate amount of ultra-large multimers released and the consequence is binding to platelets causing platelet aggregation and microthrombi. In support of this mechanism,[18,19] Miodownik et al[20] have shown that congenital thrombotic thrombocytopenic purpura can present with clinical complications during pregnancy and maternal vascular lesions of under-perfusion in the placenta.

The clinical presentation of DIC can be either thrombosis and/or bleeding as it is a thrombohemorrhagic disorder.[21] This may be explained by the extremely rapid pace of thrombin generation in the thrombotic phenotype, while it is relatively slower in the haemorrhagic presentation of this complication (Figure 1). The "hyperfibrinolytic" form of DIC as often observed in postpartum DIC, and abruption[22] results from an extremely rapid burst of thrombin generation, whereas a "procoagulant" form of DIC (eg, pre-eclampsia related DIC) may result from an excessive but slower and more gradual form of thrombin generation.[23] Although both procoagulant and hyperfibrinolytic processes may proceed simultaneously in DIC, the clinical presentation of thrombosis or bleeding is determined by the predominant mechanism at a particular time.[24]

Various obstetrical disorders can present with DIC as a complication; thus, increased awareness is key to diagnosing the condition. DIC patients can present to clinicians who may not be experienced in a variety of aspects of thrombosis and haemostasis. Hence, DIC diagnosis is often only entertained when the patient already developed uncontrollable bleeding or multi-organ failure, all of which represent unsalvageable scenarios.[25] Beyond the clinical presentations, the main issue with DIC diagnosis is in relation to coagulation test abnormalities. It is widely believed that in DIC, patients will have thrombocytopenia, prolonged prothrombin time (PT) and partial thromboplastin time (PTT), low fibrinogen and raised D-dimers.[26] These lab markers were considered as diagnostic of DIC in an era when the DIC diagnosis was predominantly made
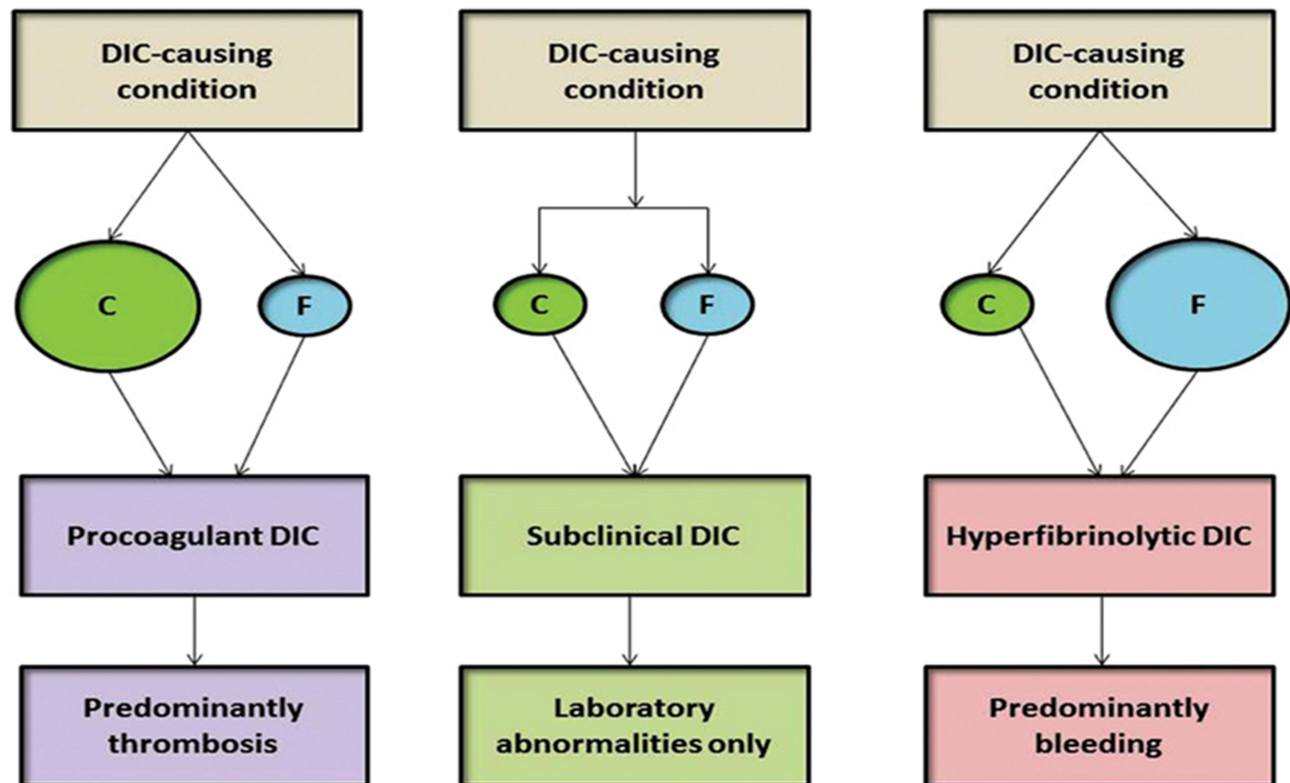
The different types of DIC

Figure I The different types of DIC and their clinical presentation. If there is predominance of coagulation pathway activation (denoted as C), in comparison with the fibrinolytic pathways (denoted as F), procoagulant DIC is the result. While the reverse leads to hyperfibrinolytic DIC.
Notes: Reprinted from: Thachil J. The Elusive Diagnosis of Disseminated Intravascular Coagulation: does a Diagnosis of DIC Exist Anymore? *Semin Thromb Hemost.* 2019;45:100–107.[24] With permission. Copyright © Georg Thieme Verlag KG.

post-mortem or in extremely ill patients.[9] The introduction of DIC scoring discussed below generates cut off values of laboratory tests that enable the clinicians to diagnose DIC at early stages of the disease with a more subtle abnormalities of the laboratory tests.

Epidemiology of DIC in Pregnancy

DIC has a higher lifetime prevalence in men than in women, the only period where the incidence of this disorders is similar between the genders is during women's reproductive years.[1] The prevalence of obstetrical DIC differs worldwide ranging from as low as 0.03% in North America to 0.35% in developing countries.[2–5,27–29] Differences in quality and accessibility to advance maternity care, as well as inconsistent definitions and diagnostic criteria led to variations in the reported incidence of DIC. Indeed, a cohort from the Nationwide Inpatient Sample from USA,[30] reported that the prevalence of DIC during

pregnancy from 1998 to 2009, increased by 35% from 0.092% to 0.125%[30] and linked with nearly a quarter of maternal deaths. Furthermore, DIC was the second most common severe maternal morbidity indicator in the USA between 2010 to 2011, affecting 32 per 10,000 delivery hospitalizations.[31]

DIC is always secondary to an underlying disorder. Indeed, it is associated with pregnancy complications such as placental abruption, HELLP syndrome, preeclampsia, retained stillbirth, sepsis, post-partum hemorrhage (PPH), acute fatty liver, and amniotic fluid embolism (Figure 2). The proportions of the contribution of each risk factor varies among countries. Indeed, the most frequent pregnancy complication associated with DIC according to Rattray et al[4] was placental abruption followed by PPH and preeclampsia. Similarly, Erez et al[5] reported that placental abruption was the leading underlying obstetrical disorder leading to DIC especially when it

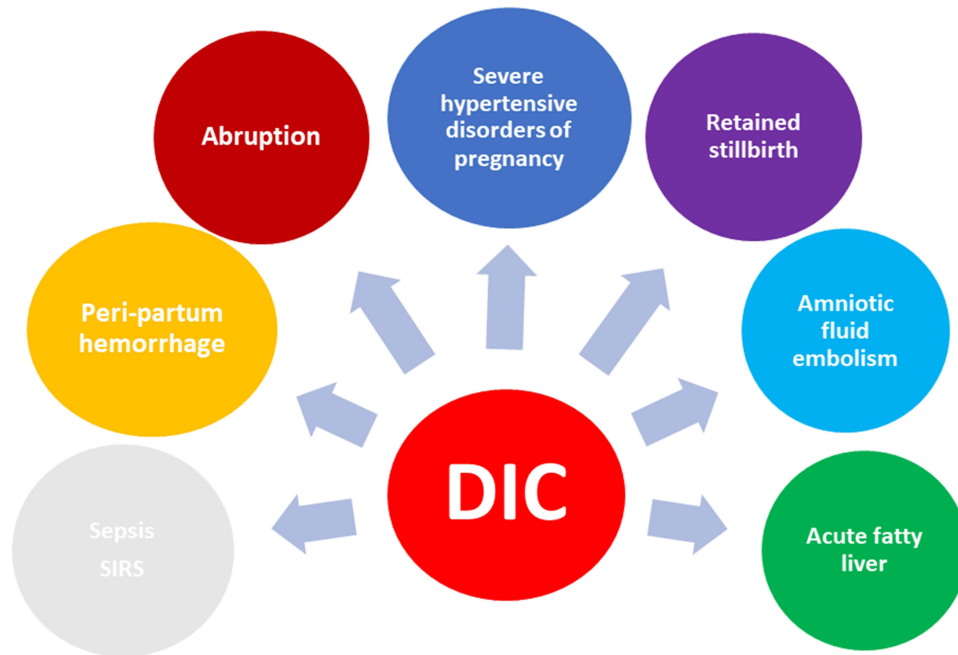## Obstetrical complications associated with DIC

Figure 2 Obstetrical complications associated with DIC in pregnancy.

was accompanied by fetal death. Other groups reported preeclampsia[32] and fetal death[29] to be the leading obstetrical complications associated with DIC (Figure 3). This suggests that early recognition and treatment of complications such preeclampsia or stillbirth may prevent the deterioration to DIC in these patients. Moreover, in countries

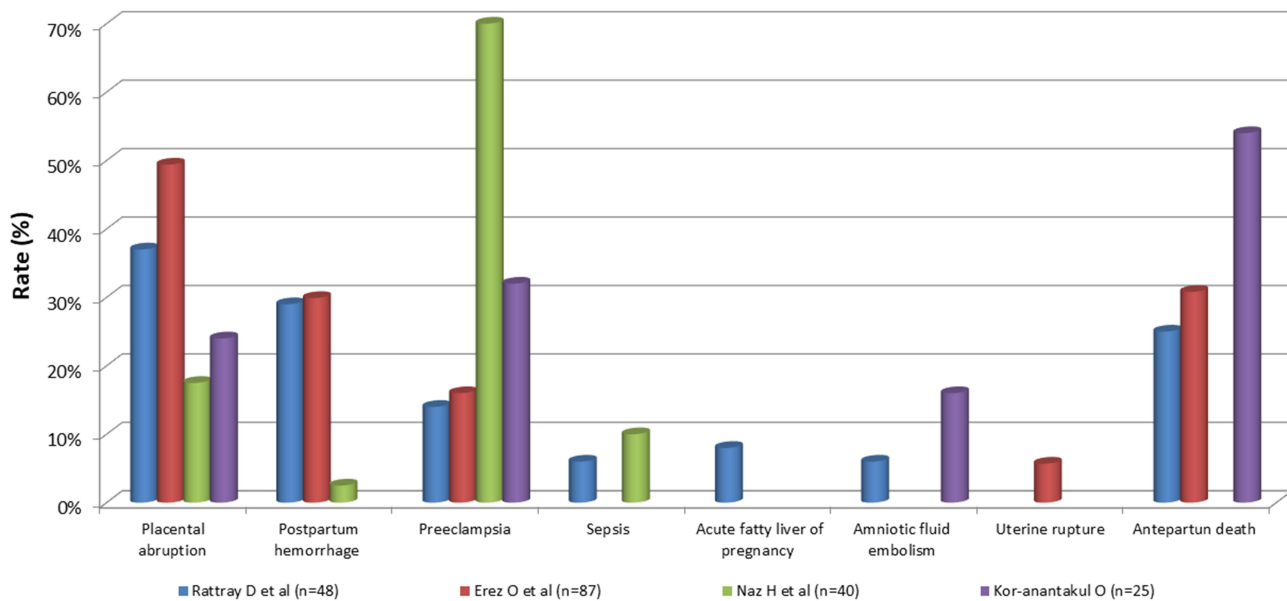## Variation in pregnancy complications resulting in DIC in different countries

Figure 3 Global distribution of obstetrical complications associated with DIC in pregnancy.
Note: Data was modified from references 4, 5, 26 and 32.

with early recognition and treatment of preeclampsia and stillbirth, placental abruption (usually unexpected and non-preventable), becomes the leading obstetrical complication associated with DIC.

Placental abruption seems to be the underlying mechanism for the development of DIC when it is associated with other obstetrical complications including fetal death and HELLP syndrome.[7,33–39]

Thus, pregnancy is a time point in women's life in which she is at increased risk to develop DIC as a result from different complications of pregnancy, and especially placental abruption. Prompt attention and treatment of underlying obstetrical disorders and rapid diagnosis and management of placental abruption can reduce the risk for DIC substantially.

Pathophysiology of DIC in Pregnancy

DIC has a complex pathophysiology, the understanding of the normal haemostasis and the highly orchestrated balance involving the various pathways including procoagulant/anticoagulant, fibrinolytic/antifibrinolytic and platelet/von Willebrand factor axis during pregnancy, is essential for the characterisation of the haemostatic abnormalities observed during DIC.[17]

Excessive and uncontrolled in vivo thrombin generation is a key to the development of DIC.[21] The excess thrombin generated will activate these pathways in differential manners. Hence, if the procoagulant and antifibrinolytic pathways are both activated "in excess", then the result would be thrombosis, especially if the natural anticoagulants have also been consumed.[25] If the excess thrombin generated drives the fibrinolytic pathway "in excess" of the other pathways, bleeding will commence.[9]

How does this translate to obstetrical cases? In the placental circulation, maintenance of the blood flow is paramount to ensure adequate oxygenation and nutrition of the foetus.[16] At the same time there is local physiological activation of coagulation in the placental bed, in preparation to quench large amounts of bleeding anticipated during parturition.[16] Despite the heightened coagulation, clots are not formed in the placental bed except in cases of abnormal placental pathologies.[40] In obstetrical disorders, the much-enhanced coagulation process could lead to microvascular clots which impair the appropriate development of the fetus.[40] In addition, if the activated procoagulant pathway does not come to a halt, this would spill into the maternal circulation causing systemic coagulopathy, otherwise termed as DIC.[24] While, if there is

a brisk fibrinolytic response, then this could lead to haemorrhage wherein formation of firm and dense clots is prevented by fibrinolytic proteins.[41] Furthermore, D-dimers and fibrin-degradation products that results from fibrinolysis interfere with platelet activation and can impair myometrial contractility.[42]

Pathological Mechanisms of DIC in Pregnancy
Endothelial Dysfunction and Platelet Activation

Normal pregnancy is associated with activation of maternal leukocytes[43] into a state akin to sepsis.[44] Nevertheless, placental trophoblast maintain a balanced systemic maternal inflammation during gestation[45] by inactivation of maternal leukocytes. However, infectious agents, septic abortion, and amniotic fluid embolism[46] leading to sepsis perturbed this balance and can lead to the development of maternal DIC (Figure 4).

During sepsis the coagulation system can be activated by Endothelial cells or leucocytes (either intact, dysfunctional, or activated), platelets, and remnants of cell surfaces, inflammatory mediators and coagulation proteins participate in the processes leading to uncontrolled activation of coagulation cascade and DIC[47] (Figure 5). These cells release pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1 (IL-1) and interleukin-6 (IL-6), along with propagation of tissue factor (TF) expression on the surface of endothelial cell and leukocytes[22,48–54] that can initiate an uncontrolled activation of the coagulation cascade via the TF/factor VIIa pathway leading to thrombin generation if this coagulation response is uncontrolled it will eventually lead to DIC.[55] The most significant source of TF is not completely clear as this activator of the coagulation cascade is expressed not only in mononuclear cells in response to pro-inflammatory cytokines (mainly IL-6), but also by vascular endothelial (Figure 5), cancer cells,[53,54,56] decidua and placenta.

Despite the potency of TF as a trigger of coagulation, potent anticoagulation pathways can control and limit its activity. However, all the natural anticoagulant pathways (ie, anti-thrombin III, protein C system, and TF pathway inhibitor [TFPI]) are compromised during sepsis mediated DIC.[57] Indeed, during DIC antithrombin III concentration are markedly reduced, due to its consumption,[58] degradation (by elastase from activated neutrophils),[59] and impaired synthesis.[49] Moreover, protein C system inhibition due to decreased protein synthesis, cytokine-mediated down-regulation of endothelial thrombomodulin and a drop in the concentration of the free fraction of protein S (protein C co-factor) may further

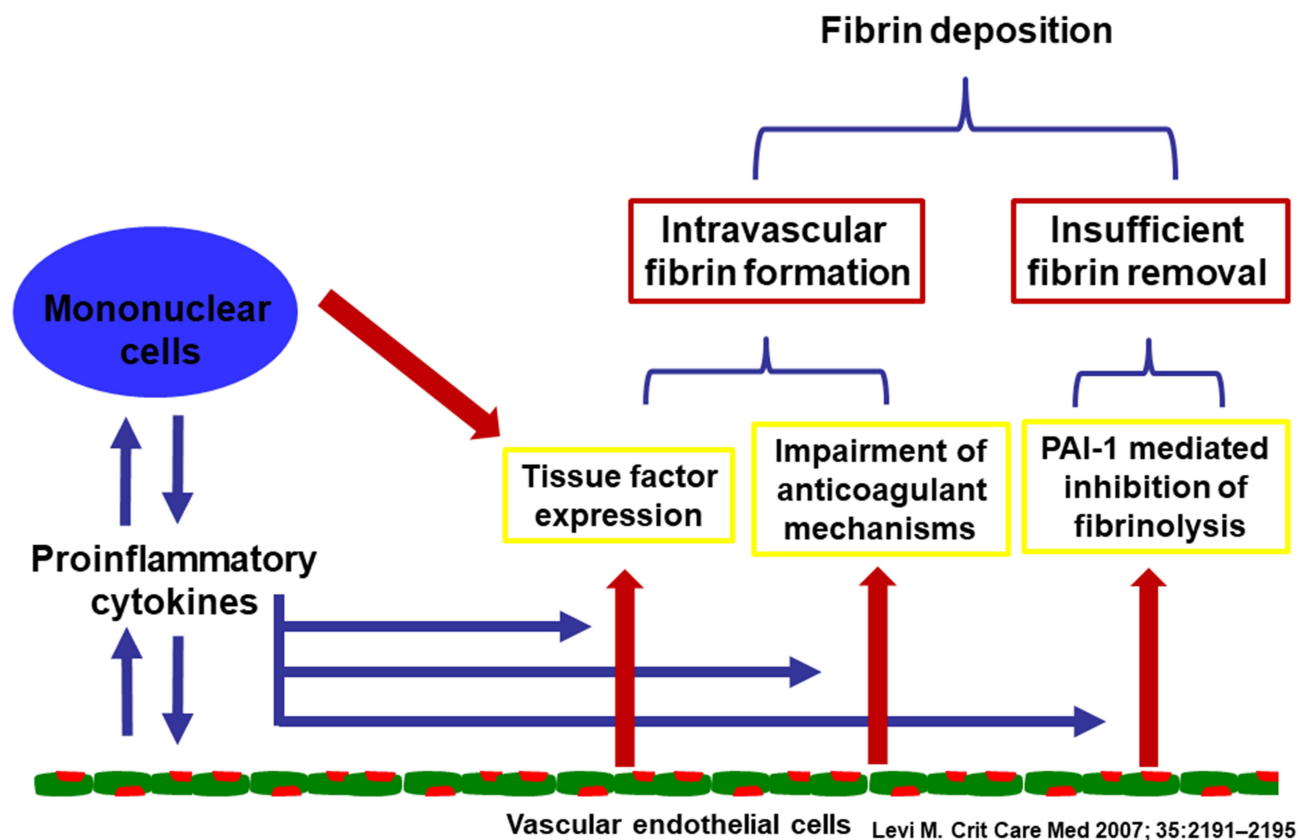## Schematic representation of pathogenic pathways in DIC

Figure 4 Schematic representation of pathogenic pathways in DIC.
Notes: Adapted from: Levi M. Disseminated intravascular coagulation. *Crit Care Med*. https://journals.lww.com/ccmjournal/pages/default.aspx. 2007;35(9):2191–2195.[49] With permission. © 2007 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins.

compromise an adequate regulation of thrombin generation.[60] Lastly, reduce TFPI function cannot address the increased activation of the extrinsic coagulation cascade.[61]

Fibrin formation in increased during DIC at the time of maximal activation of coagulation due to the following: 1) there is a continuous elevation of plasminogen activator inhibitor-1 (PAI-1) that suppresses fibrinolysis;[49,62] 2) platelets activation[63] increases TF expression on monocytes especially in the presence of granulocytes in a P-selectin dependent reaction.[56] This effect can be attributed to the induction of nuclear factor kappa B (NF-kB) activation following the binding of activated platelets to neutrophils and mononuclear cells.[64] Similar mechanisms are activated during DIC in pregnancy resulting from sepsis or systemic maternal inflammation.

Systemic inflammatory response resulting from maternal infection is not unique only for bacterial infection. Indeed, maternal DIC associated with COVID-19 infection

was previously reported.[65] Unlike the procoagulant DIC in the non-pregnant state,[66] during pregnancy, COVID-19 coagulopathy in the third trimester was associated with a clinical manifestation mimicking normotensive HELLP syndrome associated with thrombocytopenia and elevated liver enzymes[65] and the coagulopathy was of the hyper fibrinolytic type with fibrinogen concentrations and bleeding.[67] This issue is further discussed in a Communication regarding COVID-19 coagulopathy in pregnancy from the ISTH SSC for Women's Health.

Trophoblast Deportation and Systemic Activation of Maternal Coagulation Cascade

During normal gestation, the trophoblasts face two contradicting hemostatic functions: 1) sustaining of laminar flow of maternal blood in the intervillous space without clotting; and 2) to prevent bleeding at the maternal fetal interface.[9] This led to the acquirement of endothelial
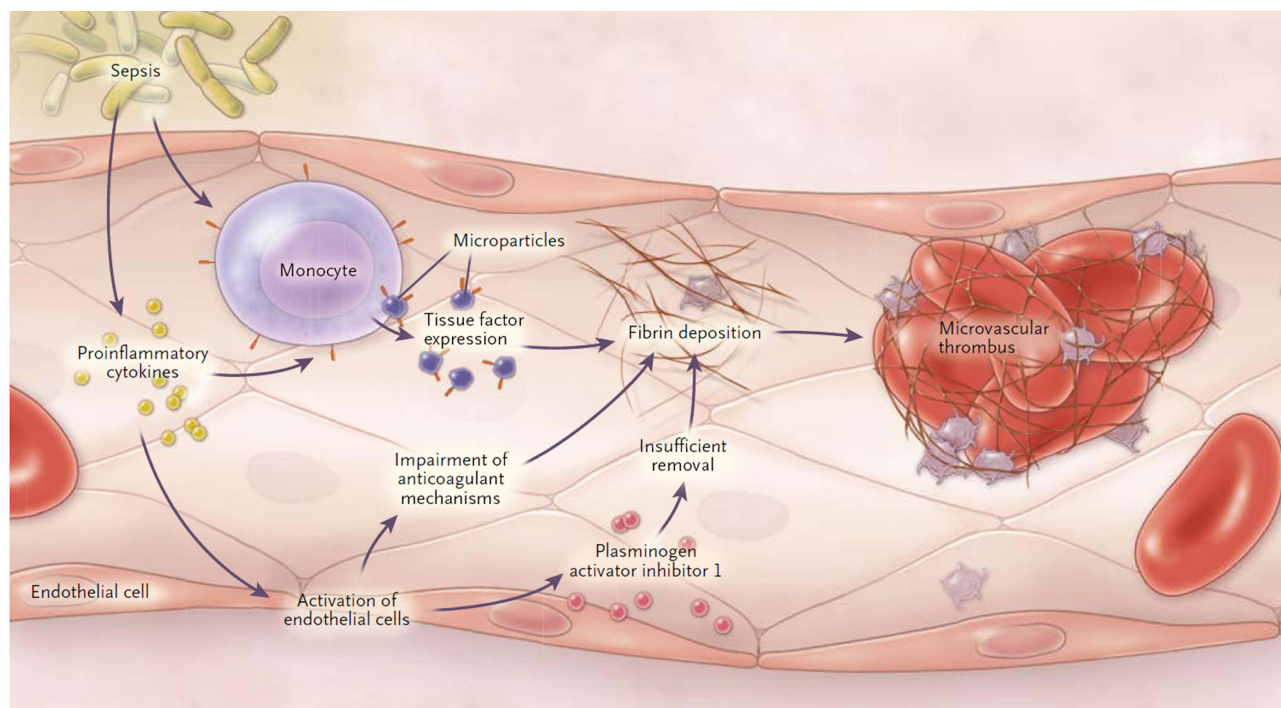
Figure 5 Mechanisms of DIC in sepsis involving endothelial dysfunction and platelet activation.
Notes: Reproduced from: Hunt BJ. Bleeding and Coagulopathies in Critical Care. *N Engl J Med*. 2014;370:847–859.[199] Copyright © 2014 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

cell like properties to the syncytiotrophoblast along with the expression of TF to maintain hemostatic function. Placental TF has higher activity in comparison to that expressed on human umbilical vein endothelial cells. The syncytiotrophoblast has also anti coagulation properties as it is able to synthesize Protein C, Protein S and Protein Z as well as pregnancy specific inhibitor of the tissue factor pathway known as TFPI-2 (Placental Protein 5)[68–70] to prevent uncontrolled activation of the coagulation cascade.[71–74] The prevention of fibrinolysis by the placenta is achieved by placental production of PAI-2 during normal pregnancy.[75] These physiological changes during pregnancy are associated with relatively constant tissue plasminogen activator (t-PA) concentrations, leading to a prothrombotic state related in part to reduced clot lysis.[76]

Disruption of trophoblast/decidua integrity would lead to a discharge of potent TF into maternal circulation, and activation of coagulation cascade that in large quantities can lead to uncontrolled systemic thrombin generation and DIC[22,77](Figure 6).

Abruption of the placental is the classica example for this mechanism, especially in cases of concealed abruption or when it is complicated by stillbirth. Even though some

regard that consumption coagulopathy as the underlying mechanism of placental abruption associated DIC, it seems that there is more to it. Indeed, women with a retro placental clot have a faster developing and more severe form of DIC than those with PPH although they have overall lower blood loss. Indeed, patients who develop placental abruption suffer from a combined coagulopathy incorporating consumption coagulopathy and substantial release of thromboplastin (tissue factor) into the maternal circulation.[9,49] In addition, local hypoxia and hypovolemia trigger endothelial response leading to increased expression of vascular endothelial growth factor, which causes an increased endothelial expression of TF.[78] This view is supported by the following: 1) Erez at al[22] reported that among women with stillbirth, those with abruption, have higher amniotic fluid TAT complexes concentrations and 2) mice who were injected with placental extracts developed DIC and died. The authors also demonstrated that administration of heparin prevented the death of the injected mice.[79] Further study suggested that thromboplastin triggers this response in mice via its effect on clotting time and chemical properties.[79] Recent advances in the understanding of the mechanisms of DIC in HELLP syndrome suggest that abruption rather than liver dysfunction
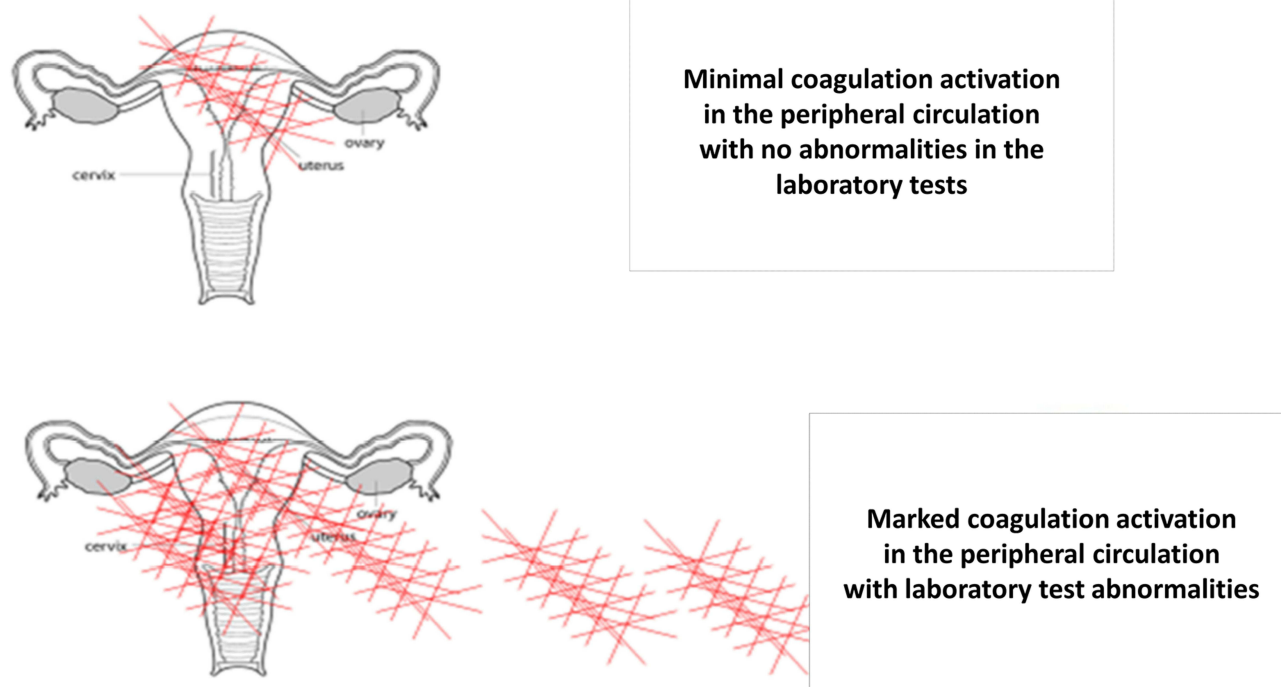
Figure 6 Trophoblast deportation and systemic activation of maternal coagulation cascade. Coagulation system is activated in the placental circulation in the normal pregnant state. This activated coagulation can spill into the peripheral circulation in patients who have obstetrical complications like pre-eclampsia. If coagulation activation in the peripheral circulation becomes uncontrolled, it manifests as DIC.

is the driving force for the development of DIC in these patients.[39] Indeed, the rate of placental abruption was 5.6% in women with HELLP syndrome without DIC in comparison to 42.9% among those with DIC,[39] suggesting that the main underlying mechanism leading to DIC in HELLP syndrome is related to trophoblast deportation into maternal circulation rather than to an intrinsic liver dysfunction.

Amniotic fluid embolism, although rare, is a major cause for maternal DIC, though a combined mechanism of activation of coagulation by the TF rich amniotic fluid debris that enter the maternal circulation and the acute systemic maternal inflammatory response further propagating the activation of the coagulation cascade. These patients have a fibrinolytic type of DIC[80] observed as unlike placental abruption autopsies of women who died due to amniotic fluid embolism lack evidence of fibrin deposition.[81] Moreover, Beller et al[82] studied the clotting and fibrinolytic systems of their patient in three blood samples: the first was drawn on admission, the second at the onset of shock and the third at the start of cardiac massage following cardiac arrest. Clotting parameters on admission were normal. The blood in the third sample did not clot even after adding thrombin in excess. Moreover,

the clotting time remained prolonged after fibrinogen was added in the presence of excess thrombin indicating that anti-thrombin activity was present. However, protamine sulfate did not restore the clotting time to normal, indicating that the antithrombin activity was not attributable to heparin. The contribution of systemic maternal inflammation to the development of DIC in women with amniotic fluid embolism is highlighted in the report of three cases of amniotic fluid embolism in which the patients had elevated maternal circulation TNFα upon admission prior to the clinical presentation of this complication.[46]

Obstetrical Hemorrhage

Hemorrhage, especially post-partum is regarded by many[4,9,50,83–87] as one of the major causes for DIC in pregnancy. Classically related to PPH, this type of consumption coagulopathy is a complication of uterine atony or rupture, retained placenta or membranes, placenta accreta, or severe lacerations of the birth canal (cervical or vaginal).[5,88,89] The characteristics of the DIC developing in these cases are the rapid maternal loss of a large blood volume along with its coagulation factors, resulting in patients who are hemodynamically compromised. Currently, there is a debate whether this form of

consumption coagulopathy is truly DIC or just a massive blood loss that depletes the patient's coagulation factors and can lead to death due to exsanguination.[90] However, maternal coagulopathy associated with PPH is not just the loss of blood volume and coagulation factor but rather a more complex complication that can be considered as DIC. This can be attributed to the procoagulant state and increased thrombin generation associated with parturition attributed to the release of TF to the maternal circulation following the separation of the membranes and the placenta;[91] along with the systemic inflammation accompanies the process of labor and delivery.[92,93] Indeed, women who had PPH are considered at high risk for development of deep vein thrombosis during the puerperium.[94] The evidence brought herein, that parturient with PPH have a higher activation of coagulation cascade, beyond physiologic levels for normal pregnancy, suggest that the clinicians who treat these patients must consider them as high risk groups for DIC, even though the fundamental pathology is considered to be the rapid and massive loss of blood and coagulation factors.[77] Therefore, PPH requires a careful and prompt assessment and to be treated pharmacologically and/or surgically, and by blood products as well as volume expanders to sustain the maternal circulation in an attempt to prevent the subsequent development of DIC.

Disruption of Liver Function

Acute fatty liver of pregnancy is severe, but a rare unique complication of pregnancy mostly observed in nulliparous patients toward the end of the third trimester.[95–97] Clinicopathological features of this complication include progressive loss of liver function,[98] abnormal renal function[99] and DIC.[100] The liver presents accumulation of fatty microvascular infiltration of hepatocytes with, without alteration of the overall structure of the liver.[98] Nevertheless, the synthetic function of the liver is hampered leading to lower production of fibrinogen and coagulation factors and along with the hemorrhage observed in this syndrome lead to DIC. Indeed, in one of the largest series of acute fatty liver published thus far including 51 patients,[101] and 80% of these women according the ISTH DIC score[102,103] had DIC similar to the report of Vigil-De Gracia et al[100] in which DIC was present in >70% of the patients. The characteristics of the hemostatic parameters of women with DIC in the study of Nelson et al[101] demonstrated that patients with DIC had persistent decreased plasma fibrinogen for several days following delivery and mild to moderately elevated fibrin

degradation products.[101] Unlike women with abruption that their hemostatic parameters recover within hours after delivery those with acute fatty liver requires several days for this to happen as a function of the recovery of the synthetic function of their liver. Thus, DIC is a central component of acute fatty liver and in a way reflects the severity of the hepatic injury.

Collectively, the alteration in maternal physiology associated with pregnancy is further augmented by different pregnancy complications leading to perturbation of the hemostatic system and the development of DIC. It is important to understand the underlying mechanisms associated with the development of DIC in each complication as it will assist the clinician in the prevention and management of DIC in these cases.

Diagnosis of DIC in Pregnancy: Clinical Definitions, Laboratory Findings and Scoring Systems

The determination whether obstetrics coagulopathy results from consumption of coagulation factors, their loss due to uncontrolled bleeding, or both. Isolated intravascular consumption of coagulation factor is a true DIC, whereas their loss due to perfused obstetrical hemorrhage can be regarded as dilutional/consumption coagulopathy. However, it is very hard to make such distinction.[25]

The hallmark of successful management of this dire complication depends on prompt and accurate recognition of DIC. Unfortunately, often the diagnosis of DIC by the attending physicians is based mainly on clinical presentation of the patient and often made relatively late in the course of the disease. During pregnancy, there is a physiologic change in the maternal plasma concentrations of many of the coagulation parameters leading to a false perception that the status of the coagulation system is normal in cases when the patient is already developing coagulopathy. Moreover, often there is underestimation of the amount of bleeding and the relevant laboratory test are performed too late when the patient is already compromised. It is important to emphasize that there is no single laboratory or clinical test that is sensitive and specific enough to diagnose DIC and the risk to develop DIC is not evident in all cases.[4,9,40,46,50,90,104] DIC is a dynamic situation that requires a continuous assessment of the clinical and laboratory parameters including decreasing concentration of fibrinogen and platelet count, prolongation of prothrombin time, and increased concentration of

fibrin split products or d-dimers[14,105,106] until it resolves. For those reasons, there is a need to: 1) develop means for early diagnosis of DIC by clinicians; and 2) establish a universal definition of DIC in pregnancy. The development of DIC scores was an effort to address both challenges. Such scores need to be simple, easy to perform, and readily available to clinicians worldwide. Indeed, these scores use simple and readily available coagulation tests including platelet count, prothrombin time (PT) prolongation, fibrinogen, and fibrin split products/D-dimer concentrations.

The use of DIC scoring systems was introduced to facilitate the diagnosis of DIC. The ISTH DIC score was proposed in 2001[102] followed by that of the Japanese Association for Acute Medicine (JAAM) in 2005,[107] both scores have good prediction performance for the diagnosis of DIC and the identification of critically ill non-pregnant patients and their prognosis in intensive care units.[103,108–110] None of these scores is adjusted for the physiologic hemostatic changes occurring in pregnancy, limiting their applicability during gestation.

Pregnancy is associated with adaptive changes in the coagulation system that are aimed to address the challenges posed by the need to have extra circulatory maternal blood flow through the placental bed. Thus, the mother has to protect herself from a life-threatening bleeding especially during labor and delivery on one hand, and secure a continuous blood flow through the placental bed to nourish the developing fetus on the other hand.[91,111–114] The adaptive changes in the hemostatic system are observed in the maternal circulation, placental bed and amniotic fluid as summarized in Table 1. Women with a normal pregnancy have: 1) excessive thrombin generation;[114,115] 2) increased agonist derived platelets aggregation;[116,117] 3) two to three fold increase in fibrinogen concentrations; and 4) towards term they experience a 20% to 1000% increase in factors VII, VIII, IX, X, and XII,[118] as well as up to 400% increase in von Willebrand factor.[118] By contrast, factors XIII and XI concentrations decrease during gestation and those of factors II & V unchanged.[119] The excessive thrombin generation observed during normal pregnancy,[114,115] is supported by the observations of elevation in circulating maternal fibrinopeptide A, prothrombin fragments (PF) 1 and 2, and thrombin–antithrombin (TAT) III complexes during pregnancy,[91,120–122] especially at the time of and after normal labor[123,124] and delivery,[121,124] subsequently, in the course of the puerperium their concentrations decrease.[124] Pregnancy is also associated with changes in the anticoagulation proteins concentrations. Indeed, there is a 55% decline in free protein S plasma concentration reaching a nadir at birth leading to an increase in resistance to activated protein C[118,125]. This process is exacerbated by cesarean delivery and infection.[118,126] The concentrations of PAI-1 increase by 3 to 4-fold during pregnancy while plasma PAI-2 values, which are negligible before pregnancy reach concentrations of 160 mg/L at delivery.[118] Thus, pregnancy is associated with increased clotting potential, as well as decreased anticoagulant properties, and fibrinolysis.[92] In addition to the changes in maternal circulation, pregnancy is associated with changes in the local hemostatic mechanisms. Indeed, there is an increase in decidual and myometrial tissue factor.[93,127–129]

Table 1 Adaptive Changes of the Coagulation System During Pregnancy

Category	Increased	Decreased	No Change
Systemic changes			
Procoagulant factors	I, V, VII, VIII, IX, X	XI	
Anticoagulation proteins	Soluble TM	PS	PC
Adhesive proteins	vWF		
Fibrinolytic proteins	PAI-1, PAI-2	t-PA	TAFI
Microparticles and antiphospholipid antibodies	MP		ALPA
Local placental changes	TF	TFPI	

Notes: Reprinted from: Brenner B. Haemostatic changes in pregnancy. *Thromb Res*. 2004;114(5–6):409—414.[198] With permission from Elsevier. doi: 10.1016/j.thromres.2004.08.004.

Similarly, changes are observed in the chorioamniotic membranes (mainly the amnion) and in the amniotic fluid.[91,130–133]

To address the changes of pregnancy in the definition of DIC, Erez et al,[5] developed a pregnancy specific DIC score by using platelet count, fibrinogen concentrations and the PT difference – relating to the difference between the patient's PT and the laboratory control. This diagnostic performance of this score for DIC at a cutoff of ≥26 points were: 88% sensitivity, 96% specificity, a positive likelihood ratio (LR) of 22, and a negative LR of 0.125 (Table 2). To validate the score vs the ISTH DIC score, Erez et al[5] compared the diagnostic parameters of both scores in women with placental abruption (n= 684); of them, 21.93% (150/684) needed blood products transfusion and 6.29% (43/684) developed DIC. The pregnancy modified DIC score had 88% sensitivity, 96% specificity, while the modified ISTH score had at a cutoff point of 0.5 had 74% sensitivity, and 95% specificity of for the diagnosis of DIC. An independent validations of

these results was reported in a population of French women with obstetrical hemorrhage who were admitted to intensive care unit.[134] Among women with liver rupture or hematoma, pregnancy specific DIC score >26 was associated with increased blood product transfusions requirement, longer hospitalizations, and lower neonatal 1 and 5 minutes Apgar scores.[135] Moreover, a retrospective analysis of blood product transfusion requirements in patients with PPH revealed that according to the pregnancy specific DIC score, blood transfusion was unnecessary in 179 of the 279 postpartum women (64.1%) suggesting that its use may prevent unnecessary transfusions and their related risks and complications.[136] Recently, Clark et al,[137] suggested an additional modified version of the ISTH DIC score. Erez et al[138] tested the performance of this suggested scoring system on their cohort and found that this score had 14.9% sensitivity, 99.9% specificity, and a LR+ score of 14.9. Despite the good likelihood ratio score, the DIC score presented by Clark et al[137] could identify only 13 out of 87 cases of DIC in

Table 2 An Effect of Components of the New DIC Score – Results of Logistic Regression

	Effect of Individual Analytes		Effect of Individual Analytes Adjusted to Other Tests		Assigned Weight[a]
	Relative Risk	p-value	Relative Risk	p-value	
PT difference (seconds)					
<0.5	1.0		1.0		0
0.5–1	12.7	0.031	29.3	<0.001	5
1.0–1.5	27.7	0.005	68.8	<0.001	12
>1.5	60.3	<0.001	558.1	<0.001	25
Platelets (10^9/L)					
<50	3.1	0.06	89.2	<0.001	1
50–100	5.2	<0.001	56.2	<0.001	2
100–185	2.9	0.001	12.8	<0.001	1
>185	1.0		1.0		0
Fibrinogen (g/L)					
<3.0	59.0	<0.001	662.9	<0.001	25
3.0–4.0	13.4	<0.001	59.1	<0.001	6
4.0–4.5	2.4	0.320	6.8	0.03	1
>4.5	1.00		1.0		0

Notes: [a]Weight was calculated as relative risk of each of the adjusted factors to the relative risk of a factor with minimal effect. Adapted from: Erez O, Novack L, Beer-Weisel R, et al. DIC score in pregnant women–a population based modification of the International Society on Thrombosis and Hemostasis score. *PLoS One*. 2014;9:e93240.[5] Copyright: © 2014 Erez et al. Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/legalcode)

this cohort, casting a heavy shadow on the clinical utility of this score. Thus, following the study by Erez et al[5] coagulation parameters standards of non-pregnant patients can no longer use for the diagnosis of DIC in pregnant women, as "Normal" values of coagulation tests are different during pregnancy, parturition, and puerperium than in the non-pregnant state (Figure 7).

Other DIC scores in pregnancy were suggested by: 1) Terao et al[139] in 1987 developed a DIC score that included three categories, etiology, clinical manifestation, and laboratory tests (PT, fibrinogen, FDP, and platelets). The study included 77 women with DIC recruited from 100 centers in Japan. A DIC score ≥7 was considered positive and identified 90% (70/77) of the patients. Of note, this score was not validated in comparison to the normal obstetric population, and it is currently not in clinical use outside of Japan. 2) the utilization of the fibrinogen/C-reactive protein (CRP) ratio as a tool to diagnose the development of DIC among women with HELLP syndrome by Windsperger et al[140] demonstrated a good sensitivity and perform better than fibrinogen concentrations alone in these patients.

The incorporation of pregnancy specific scoring system to diagnose DIC in pregnant women is an accurate and easy to use and may assist clinicians in real time during at the Labor and Delivery wards. However, there is a need for an international consensus on the diagnostic criteria and scoring for DIC in pregnancy, this will facilitate standardization of the definition and will support international research effort in this dire complication of pregnancy.
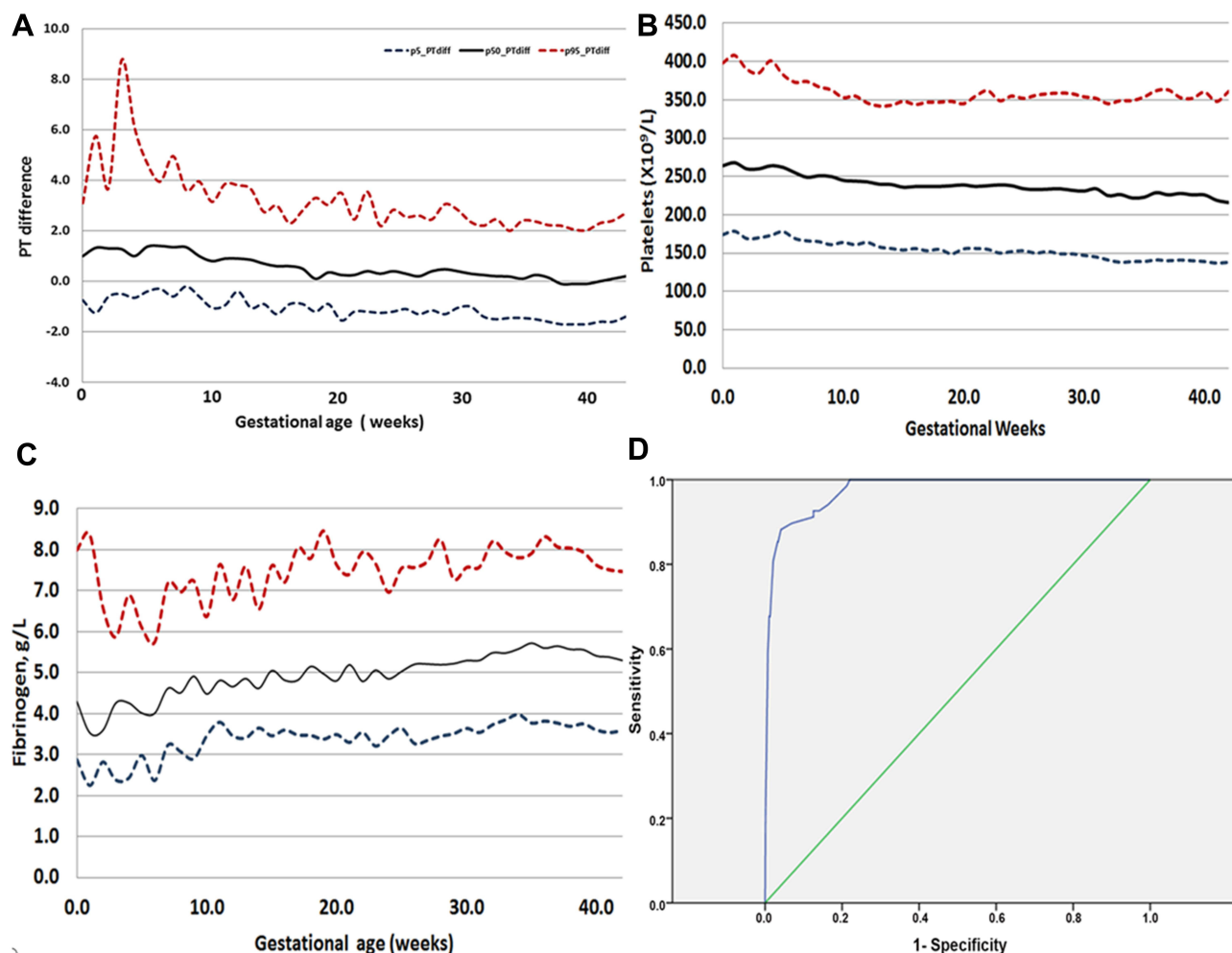

Figure 7 The changes in the major components of the pregnancy modified DIC score: (**A**) PT difference: (stands for the difference between the patients PT results and the laboratory control); (**B**) platelets; (**C**) fibrinogen, with advancing gestations in women with advancing gestation. (**D**) ROC curve analysis for the association of the pregnancy specific DIC score with the development of DIC.

Notes: Adapted from: Erez O, Novak L, Beer-Weisel et al. DIC score in pregnant women–a population based modification of the International Society on Thrombosis and Hemostasis score. *PLoS One*. 2014;9(4):e93240.[5] Copyright: © 2014 Erez et al. Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/legalcode).

Point of Care Testing in the Management of DIC During Pregnancy and Parturition

Standard laboratory tests have limitations, including absence of real-time data and incapacity to determine the functionality of the hemostatic system of whole blood (ie the strength of blood clot, and platelet function). Point of care viscoelastic tests Thromboelastography (TEG); and Rotational Thromboelastometry (ROTEM) are the most widely studied viscoelastic tests which provide a rapid assessment of in vivo coagulation. Specific TEG/ROTEM values were defined for pregnancy[16,26,84,141,142] and at the time of delivery.[143] Indeed, in comparison to the non-pregnant state, the characteristics of TEG differ significantly between pregnant and non-pregnant women, displaying a shorter R and K a higher α angle and maximum amplitude suggesting that clot formation is faster and bigger during pregnancy especially during the third trimester.[144] The ROTEM parameters display similar changes in comparison to the non-pregnant state.[145] Moreover, in a study by Rigouzzo at al[146] the TEG parameters (the maximum amplitude of K ≤63.5 mm and time to maximum rate of thrombus generation) had excellent diagnostic performance for fibrinogen concentration ≤2g/L and Platelet count ≤80,000/mm^3 in women with postpartum hemorrhage. Suggesting that TEG can be an excellent point of care testing to identify women with severe PPH at risk to develop DIC. Encouraging data show these tests may enable early detection of dysfunctional coagulation and hyperfibrinolysis,[147] allowing adequate surveillance and prompt intervention.[14,148] A study of 21 patients classified according to the ISTH DIC score, proposed a thromboelastographic score had 95.2% sensitivity, 81.0% specificity, and an AUC of 0.957 for identifying overt DIC[149] thus allowing, along other diagnostic and prognostic modalities (ie DIC scores), an adequate surveillance and, eventually, a prompt intervention during the early stages of DIC in pregnancy.[150]

Treatment of DIC in Pregnancy

Prevention, early diagnosis and treatment of obstetrical hemorrhage are the heart of midwifery.

Prevention of obstetrical hemorrhage is based on identification of patients at risk for peripartum bleeding, active management of the third stage of labor and prompt diagnosis and management of obstetrical complications that may be associated with the development of DIC even in the absence of labor, the interested reader is referred to the guidelines of the professional committees and selected reviews (ref).

The basic principles for treating obstetrical DIC are presented in Figure 8 and include the following:[9,14,106,151] 1) treatment and resolution of the underlying condition leading to DIC; 2) fast and prompt delivery or termination of pregnancy (before the threshold of viability). The delivery options should be discussed by a multidisciplinary team and consider the safest mode of delivery to the mother, how fast she is expected to deliver, what are the resources of blood products and other supportive mechanisms available, and can she sustain a surgery; 3) supportive treatment with blood product transfusion, surgical care and related measures; 4) rigorous clinical and laboratory patients surveillance; 5) prompt involvement of needed consultant such as hematologists, gynecological surgeons, anesthesiologists and others; and 6) in small to medium size health care facilities it is important to estimate whether their blood bank can support a massive blood transfusion and, if necessary, contact regional or larger hospitals for assistance or for transferring the patient.

Treatment algorithms for obstetric DIC always involve simultaneous blood product transfusion as a replacement of women's blood loss. Specific transfusion protocols have been previously published and the interested reader is referred to the specific papers on the subject.[152] The harmonized guidance from the ISTH[151,153] give a fine definition for the thresholds for blood products transfusion, and massive transfusion protocols with fixed RBC: plasma: platelet ratios,[83,152] are mostly being used, but this recommendation is under debate.[154] The response to blood component therapy should be monitored both clinically and with repeated assessments of the platelet count and coagulation parameters. For further reading, the reader is referred to the published guidelines for blood component replacement from national professional societies[155–159] and the scientific subcommittees on Women's Health Issues in Thrombosis and Hemostasis and on DIC of the ISTH.[41,160]

Viscoelastic Hemostatic Assays Guided Transfusion Protocols

During DIC there is a rapid consumption of fibrinogen and coagulation factors, making the monitoring and maintenance of proper blood products administration by conventional laboratory tests challenging, as rapid correction of blood component deficiencies is required at a rate faster than their depletion. ROTEM\TEG allow early detection and dynamic monitoring of clotting abnormalities, and
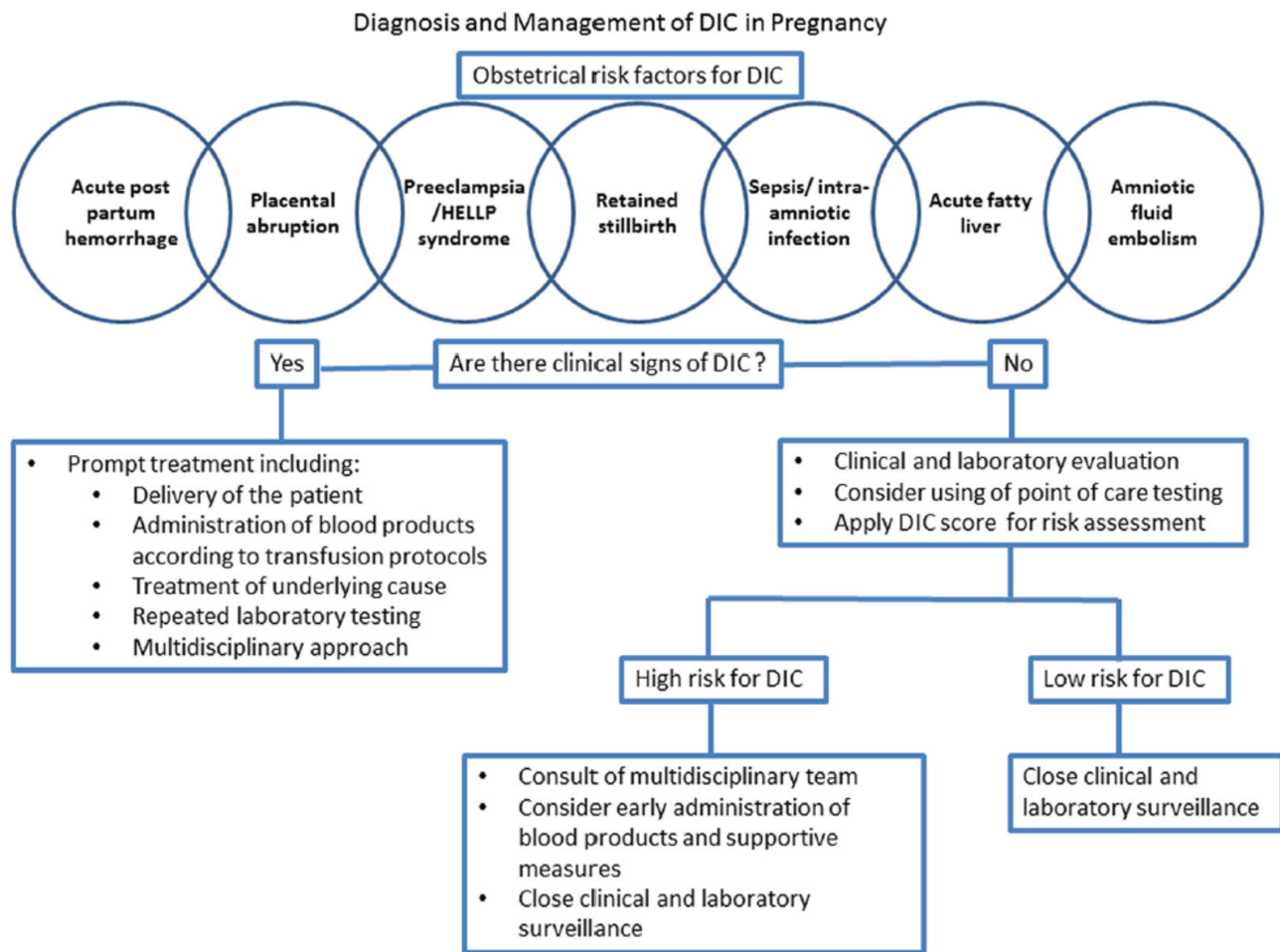
Figure 8 Principles of Diagnosis and management of DIC in pregnancy.
Notes: Reproduced from: Erez O. Disseminated intravascular coagulation in pregnancy - Clinical phenotypes and diagnostic scores. *Thromb Res*. 2017;151203 1:S56-S60.[200] With permission. Copyright © 2017 Elsevier Ltd. All rights reserved.

transfusion needed; hence, they could potentially be used as guidance for administration of blood components. Favorable evidence regarding use of these tests, especially to guide fibrinogen replacement therapy in management of obstetric complications, is accumulating.[123,147,150,161–166] Further research demonstrated that the use of ROTEM-FIBTEM A5 as a point of care testing for fibrinogen concentration assisted in targeting patients with postpartum hemorrhage who will require blood product transfusion. The rational for its use was that while Clauss fibrinogen tests results are available within an hour of venipuncture, those of FIBTEM A5 are available within 10 minutes. The authors use a FIBTEM A5 of <15 that can be translated to fibrinogen concentration of 3 grams/ Liter or 300mg/Dl as a cutoff point that requires obstetrician attention in women with PPH and developed an algorithm for the management of women with PPH based on the FIBTEM A5 results (Figure 9).[167–169] These

encouraging results in the pregnant population await further studies before widespread clinical application of VHA scan as point of care testing to guide blood product transfusion in women with PPH can be implemented.[170–173]

Another possible clinical application of VHAs could be the identification of women who show a severe hypercoagulable state and could benefit from antithrombotic prophylaxis. In a recent case-control study, Spiezia et al evaluated ROTEM profiles in women with preeclampsia in comparison to healthy pregnant women.[174] Characteristic hypercoagulable ROTEM profiles in women with preeclampsia were found.

Treatments for Coagulopathy

Based on the pathogenesis of microvascular failure and coagulation activation in DIC, strategies aimed at the inhibition of coagulation activation have been found
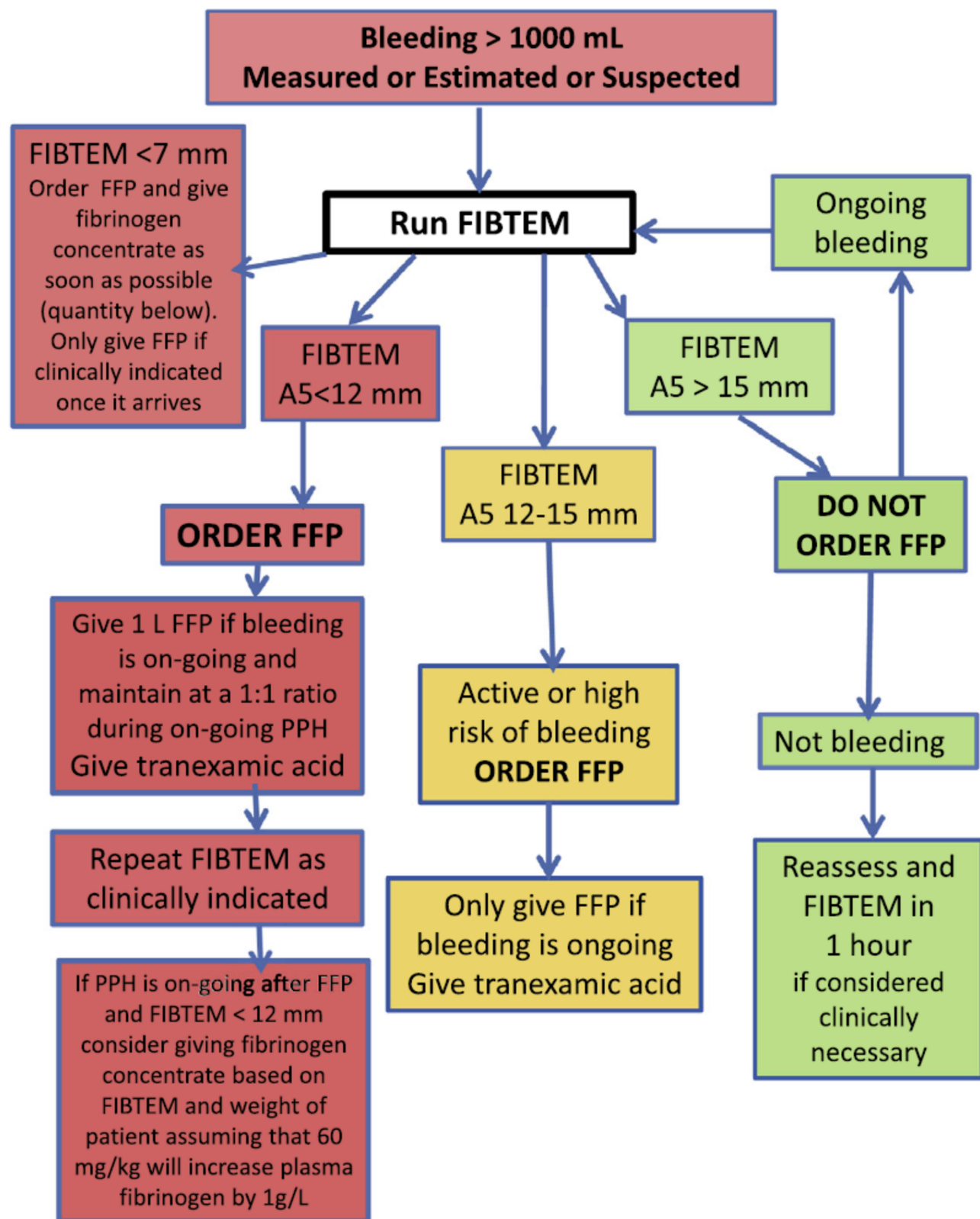
Figure 9 Algorithm for the treatment of obstetrical hemorrhage based on FIBTEM and fibrinogen concentrations.
Notes: Reprinted from: Collins PW, Bell SF, de Lloyd L, Collis RE. Management of postpartum haemorrhage: from research into practice, a narrative review of the literature and the Cardiff experience. *Int J Obstet Anesth*. 2019;37:106–117.[167] With permission Crown Copyright © 2018 Published by Elsevier Ltd. All rights reserved.

favorable in experimental and clinical studies. Most RCTs have been carried out in patients with sepsis, and evidence in obstetric DIC is limited. Tranexamic acid is used as an adjunct to blood product administration and has been studied in PPH. Recombinant activated factor VII (rFVIIa) is used as a second line treatment in women in whom massive transfusion does not halt blood loss. All other treatment modalities are considered experimental at this stage.

Antifibrinolytic Agents

Tranexamic acid (TXA) has been suggested as a treatment for coagulopathy in PPH.[175] TXA prevents the activation of plasminogen by plasmin by blocking its lysine binding sites.[175] Four recent systematic reviews of the use of TXA for reduction of blood loss in PPH came to conflicting results.[176–179] TXA appears to be a promising drug for the prevention of PPH after cesarean and vaginal delivery.[180,181] Patients with the organ failure or non-symptomatic type of DIC may not benefit from antifibrinolytic agents as fibrinolysis is needed for the resolution of widespread fibrin thromboses resulting by DIC.[182] The usual dose is 1gr administered intravenously over 10 minutes up to 4 times daily.[183]

Recombinant Activated Factor VII (rFVIIa)

Guidelines suggest that administration of rFVIIa is warranted in active obstetrical hemorrhage that does not resolve by conventional treatment or to prevent hysterectomy.[160] In such cases, this hemostatic agent decreases maternal mortality due to obstetrical hemorrhage.[184,185] A review of 99 cases of its use in DIC, of them 32 due to PPH, reported that a median dose of 67.2 mg/kg is successful in controlling the ongoing obstetrical hemorrhage.[186] Optimal use of rFVIIa requires exclusion or correction of metabolic acidosis, hypothermia, hypofibrinogenemia, and thrombocytopenia.[187] A recent RCT, reported
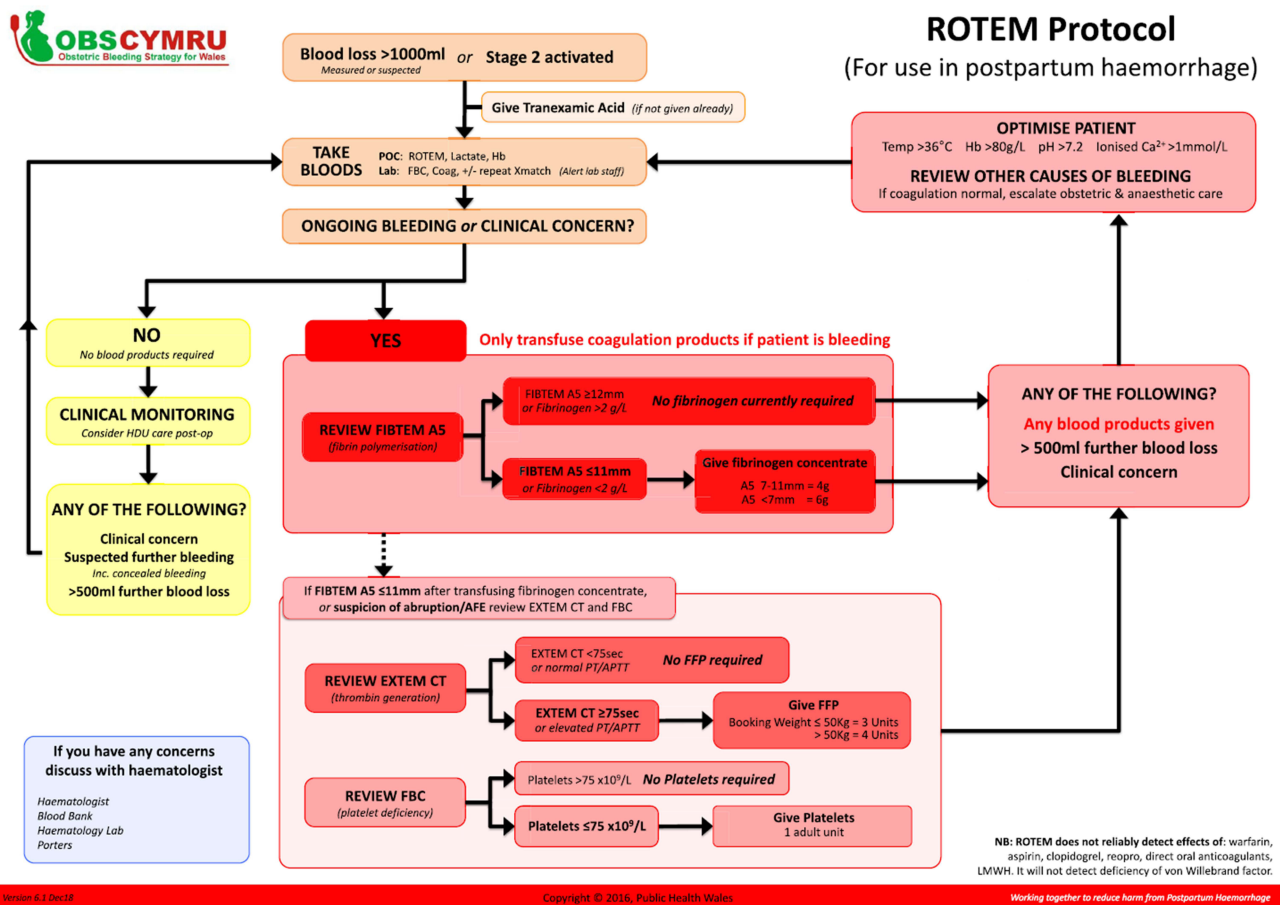

Figure 10 The ROTEM protocol of the OBS Cymru (the Obstetric Bleeding Strategy for Wales) initiative.
Notes: Reproduced with permission from: ROTEM Protocol (For use in postpartum haemorrhage); 2018. Obstetric Bleeding Strategy for Wales. Available from: https://phw.nhs.wales/services-and-teams/improvement-cymru/improvement-cymru-programmes/maternity-cymru/obs-cymru/obstetric-bleeding-strategy-cymru/rotem-point-of-care-testing.[201] Copyright © 2016, Public Health Wales.

that rFVIIa reduces by 30% the need for second-line treatments (interventional hemostatic procedures, blood transfusions).[188] However, as the use of rFVIIa increases by two fold the risk for arterial thrombosis, adequate thromboprophylaxis should be administrated to these patients following the acute hemorrhagic event. The optimal dose is unclear, however it is preferable to start with a low dose (40–60mcg/kg) to reduce the risk of thrombotic events. Higher doses (eg 90mcg/kg) can be used if the patient is unstable or if blood loss is brisk and ongoing.

Potential Experimental Treatments
Fibrinogen Concentrate
Human fibrinogen concentrates have been used for substitution therapy in cases of hypofibrinogenemia, dysfibrinogenemia, and afibrinogenemia. This product has the potential to administer relative high quantity of fibrinogen in relatively low volume of transfusion in women with obstetrical hemorrhage. Its benefits are that it is readily available, as it can be kept in room temperature or refrigerators, and it can introduce higher quantity of fibrinogen without the need to transfuse large plasma volume as in FFP transfusion.[167,189] The obstetric bleeding strategy for Wales (OBSCYMRU) initiative has adopted the use for fibrinogen concentrate at the treatment of choice for women with active obstetrical hemorrhage who has fibrinogen concentrations <2g/L or FIBTEM A5<11mm[167] (Figure 10). However, this Fibrinogen concentrate is not readily available worldwide and the current standard of care for the administration of high concentration of fibrinogen in a low volume transfusion is by cryoprecipitate. Each vial contains approximately 1000mg of fibrinogen, doses are repeated according to TEG/ROTEM guidance.

Desmopressin- 1-Deamino-8-D-Arginine Vasopressin (DDAVP)
The synthetic Anti diuretic hormone analog increases factor VIII concentrations and VWF release from endothelial cells, promoting platelet aggregation and adhesion. DDAVP can reduce bleeding resulting from obstetrical hemorrhage with a good safety profile.[190] The current evidence although limited suggest that DDAVP may be beneficial in DIC resulting from abnormal platelet activity.[191] However, it is not part of standard treatment protocols.

Recombinant Human Soluble Thrombomodulin (rhTM)
This agent was reported to potentially lower morbidity and mortality of patients with DIC due to sepsis.[192–194] This anti-coagulant reduces excessive thrombin activation and regulates the imbalance of the coagulation system. The administration rhTM to patients with obstetric DIC in a single-center, retrospective cohort study, resulted in improved platelet count, D-dimer and fibrinogen concentrations, and prothrombin time, as well as reduction in the need for platelet transfusions; however, these observations were not associated with a change in the rate of organ failure.[195] There is a need for more substantial evidence prior for the inclusion of rhTM in the treatment protocols for obstetrical DIC.

Anticoagulants
In cases of DIC with predominant hypercoagulation and thrombotic phenotype heparin can partly inhibit coagulation in this setting[196] and low molecular weight heparin (LMWH) is superior to unfractionated heparin (UFH) for treating this type of DIC.[197] However, the majority of cases of DIC in pregnancy are associated with a hemorrhagic phenotype of DIC, and heparin may increase bleeding, especially if adequate replacement therapy for consumed clotting factors has not been achieved, hence it is not recommended.

Conclusions
DIC in obstetrics is a life-threatening complication that is secondary to obstetrical and non-obstetrical related complications of pregnancy. Solid clinical and epidemiologic data is still lacking. The SSC Subcommittees on Disseminated Intravascular Coagulation (DIC) and Women's Issues in Thrombosis and Hemostasis of the International Society for Thrombosis and Hemostasis have launched a global registry of DIC in pregnancy to collect this information. We encourage physicians from across the globe to participate using this link https://redcap.isth.org/surveys/?s=KFC8RN8XWC. The diagnosis of DIC can be elusive during pregnancy and requires vigilance and knowledge of the physiologic changes during pregnancy. Pregnancy specific DIC scores and adjustment of the cutoff of point of care testing can facilitate the diagnosis and the management of DIC in pregnancy.

Disclosure
The authors report no conflicts of interest for this work.

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