J Obstet Gynaecol Barpeta. 1(2)

REVIEW ARTICLE

Disseminated intravascular coagulation in obstetrics

Rajib Kumar Bhattacharyya
Rumi Baruah [1]
Dipankar Baruah [2]

Professor and Head of Anaesthesiology & Critical Care, [1]Asso. Prof. Anaesthesiology & Critical Care, [2]Associate Professor Pathology, Fakhruddin Ali Ahmed Medical College, Barpeta, Assam, India

Correspondence Dr. Rajib Kumar Bhattacharyya; Professor and Head of Anaesthesiology & Critical Care, FAA Medical College, Barpeta. email: **drrajibbhattacharyya@gmail.com**

ABSTRACT

Disseminated Intravascular Coagulation (DIC) is an acute emergency characterized by inappropriate activation of coagulation and fibrinolytic system secondary phenomenon triggered by specific disorders such as abruptio placentae and amniotic fluid embolism due to release of thromboplastin intravascularly or endothelial damage resulting from pre-eclampsia and sepsis and manifested by severe bleeding. Diagnosis is often made from clinical manifestation and estimation of coagulation profile though histological diagnosis of fibrin deposits is the definitive feature of DIC. Basic principles of management include understanding the pathophysiology, elimination of underlying cause and replacement of lost blood and specific components.

Keywords: DIC, thromboplastin, FFP.
Conflict of interest: None. **Disclaimer:** Nil.

Disseminated intravascular coagulation (DIC) is a syndrome associated with activation of both coagulation and fibrinolytic system secondary phenomena of an underlying common obstetric conditions pre-eclampsia, eclampsia, HELLP syndrome, antepartum haemorrhage (abruption placenta), intrauterine foetal death (IUFD) more than 4 weeks, massive or incompatible blood transfusion, septic abortion or massive tissue injury, amniotic fluid embolism etc. DIC can be avoided in most cases by proper 'in time' resuscitation and management of the underlying disease in proper time, e.g. pre-eclampsia pathogenesis. There is wide spread intravascular fibrin formation in response to excessive blood protease activity that overcomes the natural anticoagulant mechanism. The exposure of blood to phospholipids from damaged tissue, haemolysis, and endothelial damage are contributing factors to the development of DIC. It is never primary, but always secondary to some general stimulation of coagulation activity by release of procoagulant substances into the blood. Fibrinolysis is stimulated by DIC, and the fibrin degradation products (FDP) resulting from the process interfere with the formation of firm fibrin clots causing a vicious circle which results in further disastrous bleeding. FDPs also interfere with myometrial function and possibly cardiac function and therefore in themselves aggravate both haemorrhage and shock. Obstetric conditions associated with DIC include abruptio

Received: 10 December 2014. **Accepted:** 20 December 2014.
Bhattacharyya RK, Baruah R, Baruah D. Disseminated intravascular coagulation in obstetrics. Journal of Obstetrics & Gynaecology Barpeta, 1(2):78-84

placentae, amniotic fluid embolism, septic abortion and intrauterine infection, retained dead fetus, hydatidiform mole, placenta accreta, pre-eclampsia and prolonged shock from any cause [1, 2].

Pathophysiology of DIC

The body is maintained in a finely tuned balance of fibrinolysis and coagulation under homeostatic conditions. The activation of the coagulation cascade yields thrombin that also converts fibrinogen to fibrin; the stable fibrin clot being the final product of haemostasis. The fibrinolytic system then functions to break down fibrinogen and fibrin. Activation of the fibrinolytic system generates plasmin (in the presence of thrombin), which is responsible for the lysis of fibrin clots. The breakdown of fibrinogen and fibrin results in polypeptides called fibrin degradation products (FDPs). The presence of plasmin is critical, as it is the central proteolytic enzyme of coagulation and is also necessary for the breakdown of clots.

The processes of coagulation and fibrinolysis are dysregulated in DIC. One critical mediator of DIC is the release of a transmembrane glycoprotein called tissue factor (TF). TF is present on the surface of many cell types (including endothelial cells, macrophages, and monocytes) and is not normally in contact with the general circulation, but is exposed to the circulation after vascular damage. For example, TF is released in response to exposure to cytokines (particularly interleukin 1), tumor necrosis factor, and endotoxin [3]. In septic conditions, this plays a major role in the development of DIC. The release of endotoxin is the mechanism by which Gram-negative sepsis provokes DIC. TF is also abundant in tissues of the lungs, brain, and placenta. This helps to explain why DIC readily develops in patients with extensive trauma.

Upon exposure to blood and platelets, TF binds with activated factor VIIa (normally present in trace amounts in the blood), forming the extrinsic tenase complex. This complex further activates factor IX and X to IXa and Xa, respectively, leading to the common coagulation pathway and the subsequent formation of thrombin and fibrin [4].

Excess circulating thrombin results from the excess activation of the coagulation cascade. The excess thrombin cleaves fibrinogen, which ultimately leaves behind multiple fibrin clots in the circulation. These excess clots trap platelets to become larger clots, which leads to microvascular and macrovascular thrombosis. This lodging of clots in the microcirculation, in the large vessels, and in the organs is what leads to the ischemia, impaired organ perfusion, and end-organ damage that occurs with DIC.

Coagulation inhibitors are also consumed in this process. Decreased inhibitor levels will permit more clotting so that a positive feedback loop develops in which increased clotting leads to more clotting. At the same time, thrombocytopenia occurs and this has been attributed to the entrapment and consumption of platelets. Clotting factors are consumed in the development of multiple clots, which contributes to the bleeding seen with DIC.

Simultaneously, excess circulating thrombin assists in the conversion of plasminogen to plasmin, resulting in fibrinolysis. The breakdown of clots results in an excess of FDPs, which have powerful anticoagulant properties, contributing to hemorrhage. The excess plasmin also activates the complement and kinin systems. Activation of these systems leads to many of the clinical symptoms that patients experiencing DIC exhibit, such as shock, hypotension, and increased vascular permeability. The acute form of DIC is considered an extreme expression of the intravascular coagulation process with a complete breakdown of the normal homeostatic boundaries.

There has been a recent challenge however to the basic assumptions and interpretations of the pathophysiology of DIC. A study of sepsis and DIC in animal models has shown that a highly expressed receptor on the surface of hepatocytes, termed the Ashwell-Morell receptor, is responsible for thrombocytopenia in bacteremia and sepsis due to Streptococcus pneumoniae (SPN) and possibly other pathogens. The thrombocytopenia observed in SPN sepsis was not due to increased consumption of coagulation factors such as platelets, but instead was the result of this receptor's activity enabling

hepatocytes to ingest and rapidly clear platelets from circulation [5]. By removing pro-thrombotic components before they participate in the coagulopathy of DIC, the Ashwell-Morell receptor lessens the severity of DIC, reducing thrombosis and tissue necrosis, and promoting survival. The hemorrhage observed in DIC and among some tissues lacking this receptor may thereby be secondary to increased thrombosis with loss of the mechanical vascular barrier. This discovery has possible significant clinical implications in devising new approaches to reducing the morbidity and mortality of DIC.

Clinical Manifestations

Related to the magnitude of imbalance of haemostasis, to the underlying disease or both, the most common findings are bleeding ranging from oozing from venipuncture sites, petichae, and ecchymosis to severe haemorrhage from GI tract or lung or into the central nervous system. The hypercoagulability of DIC manifests as occlusion of vessels in the microcirculation and resulting organ failure. Thrombosis of large vessels and cerebral embolism can also occur. Haemodynamic complications and shock are common among patients with acute DIC. The mortality ranges from 30 to > 80% depending on the underlying disease and severity of the DIC.

Diagnosis

Clinically significant DIC based on the presence of clinical and/ or laboratory abnormalities of coagulation or thrombocytopenia. No single test establishes the diagnosis of DIC. The laboratory investigations include coagulation test [APTT, PT, thrombin time (TT)] and markers of fibrin degradation product (FDP), in addition to platelet count and analysis of blood smear. The tests should be repeated over a period of 6-8 hr because initially mild abnormality can change dramatically in patients with severe DIC.

Common findings prolongation of PT and / or APTT; platelet counts< 100,000/ mm^3, or rapid decline in platelet numbers; and elevated level of FDP. The most sensitive test for DIC is the FDP level. The D-dimer test is more specific for detection of fibrin (but not fibrinogen) degradation products and indicates that the cross-linked fibrin has been digested by plasmin. Because fibrinogen has prolonged half-life, plasma levels diminish acutely only in severe cases of DIC. High grade DIC is associated with levels of anti-thrombin III or plasminogen activity < 60% normal [6].

International Society for Thrombosis and Haemostasis (ISTH) developed a more objective scoring system for the diagnosis of DIC, compared to blinded "expert" assessments for DIC, found to be 91% sensitive and 97% specific [6, 7].

ISTH scoring system for DIC

Scoring the test result as follows:

1. Platelet count > 100 x 10^9/ L= 0; < 100 x 10^9/ L= 1; < 50 x 10^9/ L= 2

2. Elevate fibrin marker (D - diamer; fibrin degradation product) No increase=0; moderate Increase = 2; strong increase = 3

3. Prolonged PT: <3 S = 0; > 3 S but < 6 S= 1; > 6 S = 2

4. Fibrinogen level > 1g/L= 0; < 1g/L= 1

Calculate score: ≥ 5 overt DIC (repeat score daily), ≤ 5 suggestive non overt DIC (repeat next 1-2 days).

Common Obsterical Complications causing DIC

a) Abruptio Placentae: DIC is more common in severe abruption with foetal death. Changes in the coagulation system depend on the extent of blood loss and, in abruptio placentae specifically, the release of procoagulant substances (tissue thromboplastins from placental injury) into the maternal circulation. Hypovolemia and hypoxia lead to an endothelial response with activated white cells and production of pro-inflammatory cytokines and oxygen free radicals. Endothelial damage and infused thromboplastins lead to widespread activation of the clotting cascade. If unchecked, there is rapid consumption of coagulation factors and platelets, with fibrin deposition in the microcirculation and in the thrombus formation on the maternal surface of the placenta, leading to defibrination, thrombocytopenia, and hemostatic failure. However, a significant

coagulation disorder can be present for some time without obvious clinical signs. Fibrinolysis is stimulated by DIC and the resultant fibrin degradation products (FDPs) interfere with fibrin clot formation exacerbating hemorrhage and negatively affecting cardiac and myometrial function. The management is aimed at treating the underlying condition itself by delivering the foetus and placenta. Maintenance of effective circulation works against the negative effects of ischemia and aids clearance of FDPs from the blood by the liver. Fibrinogen is the specific procoagulant most often needed and is administered in fresh frozen plasma. The use of heparin or antifibrinolytic agents is generally not indicated in DIC induced by abruptio placentae. Once delivery is accomplished, the process usually resolves fairly rapidly, and it is uncommon for clinically evident coagulopathy to persist beyond 12 hours after delivery [8]. However, the platelet count may only return to normal levels **2-**3 days after delivery, as time is necessary for maturation and release of platelets from the bone marrow.

b) Toxemia of pregnancy: Majority of women with preeclampsia have subclinical consumptive coagulopathy. The placenta is central to pathophysiology of preeclampsia. Placental hypoperfusion produces oxidative stress and releases circulating factors which cause activation of the vascular endothelium. Endothelial cell activation leads to liberation of vasoactive substances, decreased activity of prostacyclin and activation of clotting cascade. The levels of D-dimers are elevated in women with preeclampsia and fibrin deposition has been found on biopsies in kidneys, lungs, liver and placentae of these women. Frank DIC in hypertensive disorders occurs in association with superadded placental abruption or HELLP syndrome [9]. In preeclampsia with laboratory reports suggesting DIC, immediate delivery is recommended to avoid clinically evident DIC [10]. If expeditious delivery of baby is affected, specific treatment of DIC is often unnecessary.

c) HELLP syndrome: It may lead to disseminated intravascular coagulation (DIC). HELLP syndrome may progress to DIC in 15-38% of patients. The prothrombin time, activated partial thromboplastin time and serum fibrinogen levels are normal in HELLP syndrome but are prolonged in DIC. Evaluation of more sensitive markers of DIC, such as antithrombin III, α-2 antiplasmin, plasminogens, fibrin monomer and D-dimers, differentiates DIC from HELLP syndrome. Aggressive treatment is indicated and delivery should be expedited, by caesarean section if necessary although vaginal delivery is not contraindicated, along with control of blood pressure and coagulation abnormality [11].

d) Intra Uterine Foetal Death (IUFD): The mechanism of coagulopathy is the activation of factor VII of extrinsic pathway by the release of tissue thromboplastin from the fetoplacental unit. The association of prolonged retention of dead fetus and coagulation disorder is uncommon in modern obstetrics largely due to early aggressive treatment of intrauterine fetal demise (IUFD).The haemostatic derangements become evident after 4 to 5 weeks of IUFD. It is recommended that a complete blood count, PT, APTT, D-dimers, fibrinogen and FDPs should be done with the latter two being the earliest abnormalities to become evident. The risk of DIC in the mother after the demise of one fetus in a multiple pregnancy is negligible. A baseline coagulation profile will suffice and subsequent laboratory surveillance is probably unnecessary. However in monochorionic twin gestations there is a 12% risk of neurological deficit in the surviving fetus [12]. Low dose subcutaneous heparin is the treatment of choice for chronic low grade DIC associated with IUFD. After correction of hypofibrinogenemia to 200-300 mg/dl and platelet levels > 50,000/mm^3, delivery can be planned. In women presenting in labor, heparin is inadvisable and fibrinogen replacement may best be achieved by cryoprecipitate [9].

e) Amniotic Fluid Embolism: Amniotic Fluid Embolism (AFE) also called anaphylactoid syndrome of pregnancy, although uncommon, has become the leading cause of maternal mortality in the developed countries. The mortality rate of this condition was reported to be 60-70%, whereas the recent UK data [13] quotes

it around 24%. An anaphylactic reaction to the passage of amniotic fluid and particulate matter in the lungs results in pulmonary hypertension and hypoxia. About half of all women who survive the initial insult develop DIC. The mechanism leading to DIC in AFE is similar to that in placental abruption with the activation of factor VII of extrinsic pathway by thromboplastin like effects of fetal antigens in maternal circulation [13]. The hemorrhage of AFE is treated by volume and component replacement often in massive quantities till the correction of laboratory parameters.

f) Massive Obstetric Hemorrhage and Massive Transfusion: Dilution coagulopathy is the mechanism of DIC in these women. Massive transfusion means transfusion within 24 hours of a volume of whole blood, its components or replacement fluids greater than the total blood volume of the patient receiving transfusion [14]. Majority of healthy pregnant women can tolerate massive transfusion without developing dilutional coagulopathy or dilutional thrombocytopenia. Women receiving massive transfusion should have periodical screening laboratory tests including platelet count, PT, APTT and serum fibrinogen. Bleeding after massive transfusion is likely if PT and APTT are prolonged 1.5 times and platelet values are below 50,000/mm.3Platelet transfusions followed by FFP administration is recommended [14].

Management of severe haemorrhage

The management of the bleeding obstetric patient is an acute and frightening problem. Because of the urgency of the situation there should be a routine planned practice agreed by haematologist, physician, anaesthesiologist, obstetrician and nursing staff in all maternity units, to deal with this situation whenever it arises [15].

It is imperative that the source of bleeding, often an unsuspected uterine or genital laceration, be located and dealt with prolonged hypovolaemic shock, or indeed shock from any cause, may also trigger DIC and this may lead to haemostatic failure and further prolonged haemorrhage. The management of haemorrhage is virtually the same whether the bleeding is initiated or augmented by coagulation failure. The clinical condition usually demands urgent treatment and there is no time to wait for results of coagulation factor assays or sophisticated tests of the fibrinolytic system activity for precise definition of the extent of haemostatic failure. (Blood may be taken for this purpose and analyzed later once the emergency is over) [16].

Management of severe haemorrhage must include prompt and adequate fluid replacement in order to avoid renal shutdown [17]. If effective circulation is restored without too much delay FDPs will be cleared from the blood mainly by the liver, which will further aid restoration of normal haemostasis.

There is much controversy around which plasma substitute to give to any bleeding patient. The remarks which follow relate to the supportive management of acute haemorrhage from the placental site and/or birth canal and should not be taken to apply to those situations in which hypovolaemia may be associated with severe hypoproteinaemia such as occurs in septic peritonitis, burns and bowel infarction. The choice lies between simple crystalloids, such as hartmann's solution or ringer lactate, and artificial colloids, such as dextrans, hydroxyethyl starch and gelatin solution or the very expensive preparations of human albumin. If crystalloids are used, two to three times the volume of estimated blood loss should be administered because the crystalloid remains in the vascular compartment for a shorter time than colloids when renal function is maintained.

The infusion of plasma substitutes, i.e. plasma protein, dextran, gelatin and starch solutions may result in adverse reactions. Although the incidence of severe reactions is rare, they are diverse in nature, varying from allergic urticarial manifestations and mild fever to life-threatening anaphylactic reactions due to spasm of smooth muscle, with cardiac and respiratory arrest [18].

Dextrans adversely affect platelet function, may cause pseudo-agglutination and interfere with interpretation of subsequent blood grouping and cross-matching tests. They are, therefore, contraindicated in the woman who is bleeding due to a complication associated with pregnancy

where there is a high chance of there being a serious haemostatic defect already. Of greater significance in modern obstetric practice, acute fetal distress has been reported in mothers given dextran 70 who suffered anaphylactoid reactions [19]. These dextran-induced anaphylactoid reactions have resulted in uterine hypertonia with subsequent severe fetal bradycardia even though immunoprophylaxis with dextran hapten has been administered [20]. There are many suitable superior alternatives for plasma expansion, and the Royal College of Obstetrician recommends that dextran should be avoided in obstetric practice [21].

Many studies suggested that the best way to deal with hypovolaemic shock initially is by transfusing simple balanced salt solutions (crystalloid) followed by red cells and fresh frozen plasma (FFP) [22, 23]. Some advocate the use of a derivative of bovine gelatin polygeline (Haemaccel) as a first-line fluid in resuscitation. It is iso-oncotic and does not interfere with platelet function or subsequent blood grouping or cross-matching. Renal function is improved when it is administered in hypovolaemic shock.

The use of blood and component therapy

Whole blood may be the treatment of choice in coagulation failure associated with obstetric disorders. Fresh frozen plasma (FFP) contains all the coagulation factors present in plasma obtained from the whole blood within 6 hours of donation. Frozen rapidly and stored at -30 ^{0}C, the factors are well preserved for at least 1 year. Although cryoprecipitate is richer in fibrinogen than FFP it lacks antithrombin (AT) which is rapidly consumed in obstetric bleeding associated with DIC [23].

Platelets, an essential haemostatic component, are not present in FFP and their functional activity rapidly deteriorates in stored blood. The platelet count reflects both the degree of intravascular coagulation and the amount of bank blood transfused. A patient with persistent bleeding and a very low platelet count may be given concentrated platelets, although they are seldom required in addition to FFP to achieve haemostasis in obstetric haemorrhage. A spontaneous recovery from the coagulation defect is to be expected once the uterus is empty and well contracted, provided that blood volume is maintained by adequate replacement monitored by central venous pressure and urinary output.

If the blood loss is replaced only by stored bank blood which is deficient in the labile clotting factors V and VIII and platelets, then the circulation will rapidly become depleted in these essential components of haemostasis even if there is no DIC initially as the cause of haemorrhage. It is advisable to transfuse 2 units of FFP for every 4 - 6 units of bank red cells administered.

The single most important component of haemostasis at delivery is contraction of the myometrium, stemming the flow from the placental site. Massive transfusion of all clotting factors and platelets will not stop haemorrhage if the uterus remains flabby.

Haemostatic failure may be suspected if there is persistent oozing at the site of venepuncture or bleeding from the mucous membranes of the mouth or nose. Simple rapid screening tests, as described above and referred to below, will confirm the presence of DIC. There will be a low platelet count, greatly prolonged thrombin time, low fibrinogen, together with raised FDPs, due to secondary fibrinolysis stimulated by the intravascular deposition of fibrin.

Conclusion

The major determinant of the survival from severe obstetric bleeding in DIC is prompt identification of the underlying trigger, elimination of the cause and appropriate management. Prompt diagnosis and aggressive management with crystalloid and fresh whole blood is the key success in the management of DIC. The collection of blood for cross mating should be done before infusion colloid like haemaccel. Rapid screening test for coagulation profile seek for and repeated in next 24 hours. Initial resuscitation with crystalloid or colloid (not dextran) to prevent hypovolaemic shock till fresh whole blood available. Blood component FFP (full of clotting factors) and platelet concentrate can halt the ongoing process of DIC in any massive obstetric bleeding. In absence of blood component therapy whole fresh blood transfusion should be asked for which is equally affective in DIC.

References

1. Crowhurst JA, Plaat F. Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1994-1996. Journal of Association of Anaesthetist of Great Britain and Ireland. 1999; 54(3): 207-209.

2. Bonnar J. Massive obstetric haemorrhage. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000; 14(1): 1-18.

3. Kumar V, Abbas KA, Fausto N, Mitchell R, editors. Robbins Basic Pathology. Philadelphia: Saunders Elsevier; 2007.

4. Hoffman R, Benz E, Silberstein L, Weitz J, Anastasi J, editors. Hematology: Basic Principles and Practice. Philadelphia: Elsevier Saunders; 2012.

5. Grewal PK, Uchiyama S, Ditto D, Varki N, Le DT, et al. The Ashwell receptor mitigates the lethal coagulopathy of sepsis. Nature Medicine. 2008; 14 (6): 648 - 55.

6. Fauci SA, Braunwald E, Kasper LD, Hauser LS, Longo LD, Jameson LJ, Loscalzo J. Harrison principles & practice of medicine. 17th ed. New York: McGraw-Hill Professional; 2008.

7. Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med. 2004; 32(12): 2416-21.

8. Clark SL. Placenta previa and abruption placentae. In: Creasy RK, Resnik R, editors. Maternal-Fetal Medicine - Principles and Practice. 5th Ed. Philadelphia: Saunders; 2004. p. 707-22.

9. Dildy III GA, Michael A, editors. Critical care obstetrics. Oxford: Blackwell Science; 2008.

10. Rath W, Faridi A, Dudenhausen JW. HELLP syndrome. J Perinat Med. 2000; 28: 249-60.

11. Garg R, Nath MP, Bhalla AP, Kumar A. Disseminated intravascular coagulation complicating HELLP syndrome: perioperative management. BMJ Case reort. 2009; volume 2009.

12. Creasy R, Resnik R, editors. Maternal Fetal Medicine. Philadephia: WB Saunders; 1999.

13. Waterstone M, Bewley S, Charles Wolfe C. Incidence and predictors of severe obstetric morbidity: case control study. BMJ. 2001; 322: 1089-94.

14. Reiss RF. Hemostatic defects in massive transfusion: rapid diagnosis and management. Am J Crit Care. 2000; 9: 158-65.

15. Letsky Elizabeth A. Disseminated Intravascular Coagulation. Best Practice & Research Clinical Obstetrics and Gynaecology. 2001; 15(4): p. 623-644.

16. Hewitt PE, Machin SJ. Massive blood transfusion. In: Contreras M, editors. ABC of Tranfusion. 3rd Ed. London: BMJ Books; 1998. p 49-52.

17. Doenicke A, Grote B, Lorenz W. Blood and blood substitutes in management of the injured patient. British Journal of Anaesthesia. 1977; 49: 681- 88.

18. Barbier P, Jonville AP, Autret E, Coureau C. Fetal risks with dextrans during delivery. Drug Safety. 1992; 7: 71-73.

19. Berg EM, Fasting S, Sellevold OF. Serious complications with dextran-70 despite hapten prophylaxis. Is it best avoided prior to delivery? Anaesthesia. 1991; 46: 1033-1035.

20. RCOG Working Party. Report of the RCOG Working Party on Prophylaxis against Thromboembolism in Gynaecology and Obstetrics. London: The Royal College of Obstetricians and Gynaecologists. 1995.

21. Moss G. An argument in favour of electrolyte solutions for early resuscitation. Surgical Clinics in North America. 1972; 52: 3-17.

22. Virgilio RWK, Rice CL, Smith DE, et al. Crystalloid versus colloid resuscitation: is

one better? A randomized clinical study. Surgery. 1979; 85: 129 - 39.

23. Estelles A, Gilabert J, Espana F, et al. Fibrinolysis in preeclampsia. Fibrinolysis. 1987; 1: 209 -14.