REVIEW (Derleme)

DISSEMINATED INTRAVASCULAR COAGULATION IN OBSTETRICS: ETIOPATHOGENESIS AND UP TO DATE MANAGEMENT STRATEGIES

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SUMMARY

Disseminated intravascular coagulation related to obstetric conditions is rarely seen but is associated with high morbidity and mortality. Recently, pathophysiology of disseminated intravascular coagulation has not been understood well and, therefore, effective and permanent treatment strategies are missing. In this review, we try to discuss the etiology, current diagnostic approaches and management strategies of disseminated intravascular coagulation from the perspectives of clinicians.

Key words: *disseminated intravascular coagulation, morbidity and mortality, pregnancy*

Journal of Turkish Society of Obstetrics and Gynecology, (J Turk Soc Obstet Gynecol), *2014; Vol: 11, Issue: 1, Pages: 42-51*

OBSTETRİDE YAYGIN DAMAR İÇİ KOAGÜLASYON: ETYOPATOGENEZ VE GÜNCEL TEDAVİ STRATEJİLERİ

ÖZET

Obstetrik nedenlere bağlı olarak gelişen yaygın damar içi koagülasyon, nadir görülmesine rağmen morbidite ve mortalitesi oldukça yüksek seyreden klinik bir durumdur. Günümüzde yaygın damar içi koagülasyonun patofizyolojisi tam olarak aydınlatılamamış olup, bu nedenle etkili ve kalıcı tedavi yöntemleri henüz geliştirilememiştir. Bu derlemede, klinisyenin bakış açısıyla obstetrik pratikte karşımıza çıkan yaygın damar içi koagülasyon değerlendirilmiş ve güncel literatür bilgisi ışığında yaygın damar içi koagülasyonun etyopatogenezi, tanısal yaklaşımları ve tedavi alternatifleri tartışılmıştır.

Anahtar kelimeler: *gebelik, morbidite ve mortalite, yaygın damar içi koagülasyon*

Türk Jinekoloji ve Obstetrik Derneği Dergisi, (J Turk Soc Obstet Gynecol), *2014; Cilt: 11, Sayı: 1, Sayfa: 42-51*

INTRODUCTION

At present time, obstetrical bleedings remain to be the worldwide's main cause of maternal mortality and early identification of factors leading to hemorrhage and rapid management of the underlying pathological process is the key stone of the treatment[1]. The most important pregnancy related conditon leading to bleeding with high mortality and mobidity rates is dissemniated intravascular coagulation (DIC).

Dissemniated intravascular coagulation was first described by Joseph DeLee in 1901 as a fatal hemorrhagic diathesis following placental abruption[2]. The underlying pathophysiology in DIC is systemic activation of the

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Received: 12 May 2013, revised: 27 July 2013, accepted: 28 July 2013, online publication: 31 July 2013

DOI ID:10.5505/tjod.2014.93196

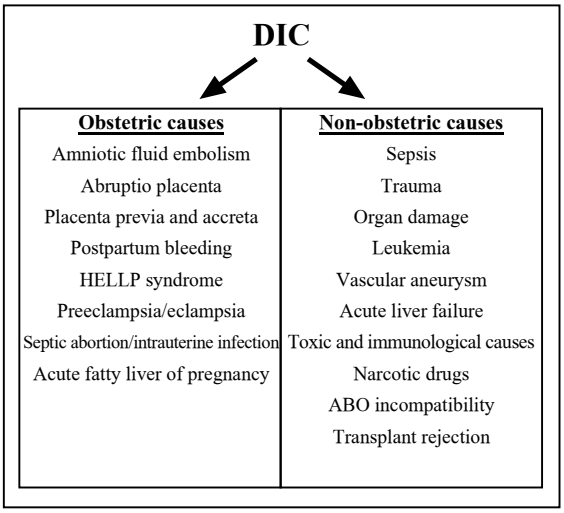
coagulation cascade leading to extensive fibrin deposition and subsequent microvascular thrombosis. Furthermore, patients exhibit a tendency for severe bleeding associated with the consumption of platelets and coagulation factors[3,4]. Clinically, DIC may lead to a wide range of pictures from unnoticed intravascular thrombosis and microvascular damage to uncontrollable bleeding. DIC always evolves secondary to predisposing clinical condition[5]. The real incidence of obstetrical DIC is unknown since it represents a wide spectrum ranging from mild to severe. Various studies done showed that the incidence of DIC in all pregnancies was 0.02-0.07 %[6,7]. Maternal mortality associated with DIC vary from 6 to 24% and postpartum hysterectomy, massive blood transfusions and acute tubular necrosis are listed as the main maternal morbidity indicators[7,8]. Therefore, early detection of these predictors of DIC and timely intervention of this life-threatening condition is very important.

CONDITIONS LEADING TO DISSEMINATED INTRAVASCULAR COAGULATION

Obstetrical and non-obstetrical etiologies leading to DIC are listed in Figure 1. In a study reported by Darrien et al, the identified causes of obstetrical DIC were listed as placental abruption (%37), postpartum bleeding (%29), severe pre-eclampsia/HELLP syndrome (Hemolysis, Elevated Liver Enzymes, Low Platelet Count) (%14), acute fatty liver of pregnancy (%8), sepsis (%6) and amniotic fluid embolism (%6)[8]. Intrauterine fetal loss is also reported as a cause of DIC[9].

Placental abruption, is a pathology charaterized by rupture of the maternal decidual artery resulting in hemorrhage into the deciudal-placental interface[10]. Although, the underlying pathophysiology is not fully understood, placental insufficiency and uteroplacental hypoperfusion are postulated to be the cause[11]. It has also been shown that pro-inflammatory cytokines cause premature seperation of of the placenta[12]. Studies reported showed a positive relationship between the degree of placental seperation and fibrin deposition as well as thrombocytopenia suggesting that the coagulation process initially starts in the placental bed[13]. Similar to trauma patient, in postpartum bleeding, the severe amount of blood loss and subsequent consumption of coagulation factors is held responsible for the development of DIC[14].

Figure 1: *The reasons of Disseminated Intravascular Coagulation (DIC).*



In pre-eclampsia, the maternal inflammatory response formed against trophoblasts results in a systemic endothelial dysfunction. Thus, vasodilator prostaglandins decrease and thrombocyte aggregation and uteroplacental ischemia increases[15,16].

HELLP syndrome, is a syndrome characterized by endothelial cell damage in the liver[17]. It is believed that substances originating in the placenta cause an acute inflammatory state in the hepatic endothelial cells[18]. This inflammatory cascade is reported to be different then the inflammatory mediators involved in the process leading to the DIC picture[19].

Septic abortion causes DIC by triggering the release of inflammatory substances which are eventually disrupting the coagulation mechanism. Studies done showed that endothelial dysfunction plays a key role in the pathophysiology of septic abortion[20].

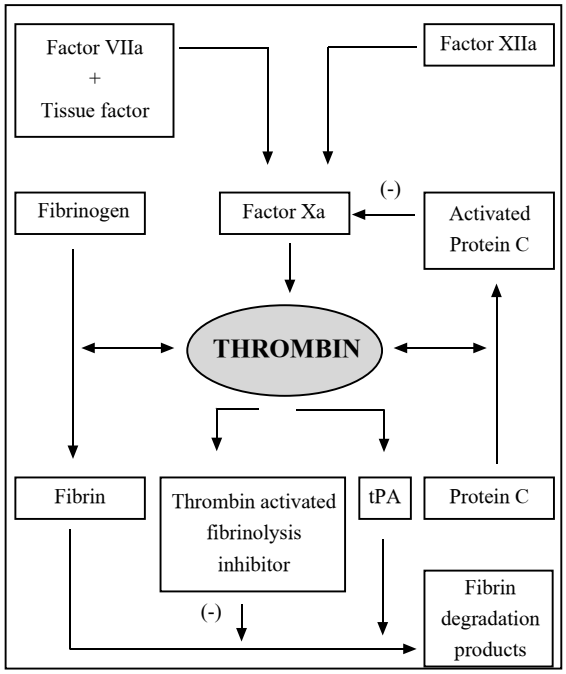
Amniotic fluid embolism, is a clinical condition that could be observed during the delivery and postpartum upto 48hrs. It has been reported that 70% of the cases occurred pre-partum[21-24]. Clinically, it's characterized as hypotension, cardiac arrhythmia, cyanosis, dyspnea, altered mental status and bleeding. Clark et al estimated the maternal mortality rate attributed to amniotic fluid emboli as 61%[22]. Recenly published studies, reported various rates ranging 6 - 44%[25,26].

Acute fatty liver is mostly reported in the third trimester and has a fulminant course. Studies done identified genetic deficiencies in the beta oxidation of fatty acids played a role in the pathogenesis of acute fatty liver[27]. Severe hepatic dysfunction and Anti-Thrombin III deficiency are hypothesized to be involved in the course of DIC[28,29].

PATHOPHYSIOLOGY

Disseminated intravascular coagulation is a systemic thrombohemorrhagic disorder developing secondary to certain clinical conditions. In order to understand the changes it is essential to have a fund knowledge of the normal coagulation mechanisms. The coagulation cascade is demonstrated in Figure 2. The coagulant response is initiated with the formation of Tissue Factor (TF) and subsequent binding to Factor VIIa. As a result, Factor X is activated and thus prothrombin is converted to thrombin (Factor IIa)[30]. Thrombin, plays a central role in coagulant, anticoagulant fibrinolytic, antifibrinolytic and antifibrinolytic mechanisms[31].

Figure 2: *tPA: tissue plasminogen activator.*



The coagulant response is initiated with the formation of Tissue Factor (TF) and subsequent binding to Factor VIIa. As a result, Factor X is activated and thus Prothrombin is converted to Thrombin (Factor IIa).

Besides being a a procoagulant converting fribrinogen to fibrin, thrombin also controls anticoagulation by activating protein C. Fibrinolysis, is degradation of fibrin to fibrin split products via tissue plasminogen acticator (tPA) activated by thrombin.

Thrombin also regulates fibronolysis by activating the active fibrinolysis inhibitor (TAFIa).

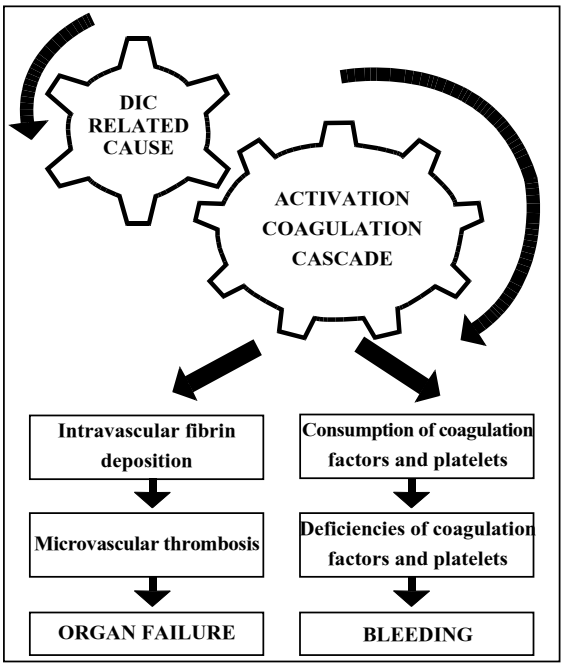
Therefore, thrombin plays a cental role in coagulant, anti-coagulant, fibrinolytic and anti-fibrinolytic mechanisms. Shows negative inhibition. bleeding (Reference #65 is used in to build this figure).

Physiological changes in the coagulation mechanisms during pregnancy

During the pregnancy substantial changes take place in the hemostasis mechanism. Significant rise in the majority of the coagulation factors, and decrease in the level of natural anticoagulants and fibrinolytic activity are the most important physiological changes notable through pregnancy. These alterations lead to a state of hypercoagulability and an increased risk of thrombembolism. Following the delivery, the period of time when the placenta is being retrieved has the highest level of thrombotic activity due to release of thromboplastic substances. Fibrinogen levels double during the pregnancy compared to prior to the pregnancy. Also, D-Dimer levels rise during the pregnancy[32-34].

In response to activation of cytokines, release of pro-coagulant factors or exposure to pro-coagulant factors, all predisposing factors leading to DIC initiate the activation of the coagulation cascade as part of the systemic inflammatory response[35]. The DIC pathogenesis is a complex mechanism in which the invivo increased thrombin production plays a central role. Increased tissue factor production, anticoagulation system dysfunction, insufficient fibrinolysis and increased anionic phospholipid concentration leads to development of DIC[36]. The pathophysiology of DIC is demonstrated in Figure 3.

Figure 3: *The Pathophysiology of Disseminated Intravascular Coagulation (DIC).*



CLINICAL FINDINGS

Disseminated intravascular coagulation is an aquired thromboembolic disease where the clinical findings usually depend on the underlying pathology. In the early stage (acute period), a massive thrombin production takes place as a result of exposure of blood to excessive amount of tissue factor. Subsequently the coagulation cascade is triggered acutely[36]. This condition can present itself with a clinical picture varying from bleeding to thrombosis. End organ damage at the microvascular level ensues as result of fibrin accumulation in the intravascular bed. The overall conditon of patients' are often critical in disseminated intrvascular coagulation along with parallellism between the findings and severity of illness. Bleeding is usually the most frequent clinical finding. It manifests itself usually as echymosis, petechia, mucosal oozing, prolonged bleeding at vein pucnture sites, surgical incision sites and from various systems, especially the gastrointestinal system. Altered mental status, acute renal failure, hypoxia and hypovolemic shock may occur as a result of blood loss[36,37]. Although, rarely seen, abdominal compartment syndrome may also be encountered in these patients. Abdominal compartment syndrome, is a condition in which tissue perfusion and organ functions are adversely affected due to increased pressures in an enclosed anatomical space leading to dysruption of the circulation. It is a clinical picture that presents itself as cardiovascular insufficiency, respiratory failure, renal dysfunction, increased intra-abdominal pressure and abdominal distension and improves with prompt surgical decompression[38].

DIAGNOSIS

There is no single laboratory test to diagnose DIC. The diagnosis is established based on clinical suspicion and supportive laboratory tests. The tests used include laboratory parameters indicative of procoagulant and fibrinolytic substance activation, inhibitor consumption and organ damage or failure[36,39].

Disseminated intravascular coagulation is a dynamic process and the tests conducted reflect only the conditions at any given moment in time. In clinical circumstances associated with this condition repeating these tests aids in establishing the diagnosis. Tests used in assessing the hemostatic state provide information about the clinical course. Prothrombin time (PT), activated partial thromboplastin (aPTT) and thrombocyte count reflect the consumption and activation of thrombocytes[40]. The laboratory finding showing fibrin production is made indirectly by measuring the fibrin degradation product, D-Dimer[41]. In a multicenter meta-analysis the most frequent encountered abnormal laboratory findings in DIC were listed as thrombocytopenia, increased fibrin degradation products, prolonged PT, aPTT and low fibrinogen levels[42-46]. In a study reported by Spero et al, thrombocytopenia was noted in 98% of patients, while severe thrombocytopenia ($<50 \times 10^9$/l) was noted in 50% of patients[45]. In another study, it was postulated that low platelet counts could be an indicator of increased thrombin production[47]. Thrombocyte aggregation related to thrombin is the the main reason of thrombocyte consumption[48].

Fibrin degradation products (FDPs) and D-Dimer are tests used in the diagnosis of DIC, however, a diagnosis of DIC can not be established based only on an elevated D-Dimer. Along with the rise in D-Dimer levels, a decrease in the thrombocyte counts and changes in the coagulation time have been accepeted as important laboratory findings of DIC[49].

A prolonged PT and aPTT is seen in 50-69% of cases[50]. This condition is related to the consumption of the coagulation factors. Since, a normal or even shortened PT and aPTT level is seen in half of the Disseminated Intravascular Coagulation cases, repeating these test in the follow-up of these patients is highly important[51].

Although, fibrinogen is a frequently used test in the diagnosis of DIC, it is considered as a less specific test[52]. Fibrinogen is an acute phase reactant and plasma levels, therefore, may run for a long period of time within normal limits independent of the consumption of coagulation factors. In a study, the specificity of low fibrinogen levels in the diagnosis of DIC was reported as 28% and hypofibrinogenemia was noted only in severe DIC cases[53]. In another study, 57% of DIC cases were noted to have normal fibrinogen levels[45]. Therefore, measurement of serial fibrinogen levels in these patients is essential as it provides us diagnostic clues.

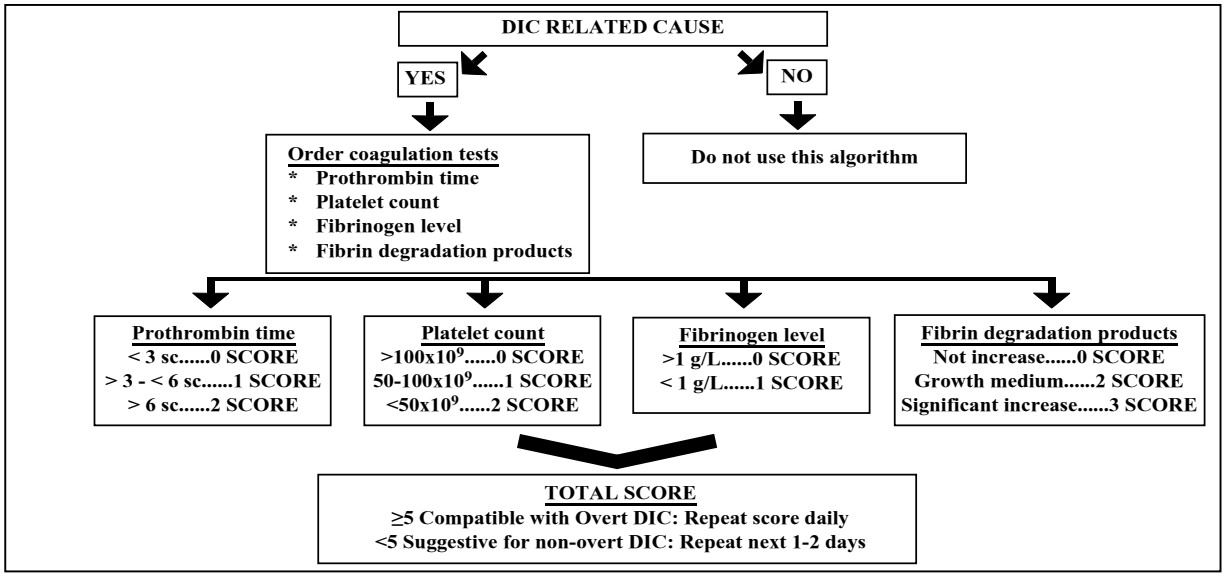
In contrast to classical DIC cases, during pregnancy, the reliability of tests used in the diagnosis of DIC is limited due to a rise in the serum levels of coagulation

factors[54]. In pregnancy, PT and aPTT levels shorten based on the increase in coagulation factors. During pregnancy, even if the consumption of coagulation factors associated with DIC leads to prolongation of PT and aPTT levels, they may still be within normal limits. For this reason, serial measurements are vital in the diagnosis of evolving DIC[55]. Similarly, physiological thrombocytopenia associated with pregnancy should be considered while diagnosing DIC. In serial analyses, the decline in platelet counts provides information about the increase in thrombin formation and the associated development of DIC[56]. Levels of Fibrinogen, an acute phase reactant, rise in pregancy. In a study analysing 535 patients with an overt diagnosis of non-pregnancy associated DIC, only 46 patients (8.6%) were noted to have a low fibrinogen level (less than 1gm/L)[52]. Considering the double fold increase in baseline fibrinogen levels during pregnancy, it is not surprising to encounter fibrinogen levels which are within normal limits in patients with a suspicion of DIC[57]. Furthermore, Fibrinogen levels are used as an indicator of the severity of portpartum bleeding[58]. Since, D-Dimer levels are already elevated in pregnancy, only a significant rise in serial measurements may aid in the diagnosis of DIC[59]. As a result of the above mentioned reason, the yield of diagnostic tools used in DIC shows a difference in DIC associated with obstetrical causes comapred with classical DIC. In methods, such as the thromboelastography (TEG) and rotational TEG (ROTEG), the path from the initiation of clot formation to fibrinolysis, including thrombocyte functions is considered as a whole[39]. In these methods, the coagulation is activated by spinning the blood in a pool. For example, a sensor placed inside, enables accurate measurements of the speed and structural strength of clot formation. Thus, activation of the coagulation systems, thrombocyte functions and analysis of fibrinolysis can be achieved. In contrast to conventional coagulation tests, in the TEG system, other than tracking the elapsed time for the clot formation, the quality of clot formed is assessed as well. Therefore, the hemostatic system is analyzed both quantitatively and qualitatively. Thromboelastography is a frequently prefered diagnostic method test as it can be performed at bedside, i.e., point of care testing (POC testing). Clinically, it's especially used in cardiac surgery and liver transplantations[60]. TEG, aids in rapid diagnosis of DIC suspected cased, providing an opportunitty to address the dysfunction in the coagulation systems[61].

Scoring used in Disseminated Intravascular Coagulation

There is no single test to diagnose DIC. The International Society of Thrombosis ve Hemostasis (ISTH) developed a scoring system for the diagnosis of DIC thus easing the diagnosis and management[62]. The flow chart of this scoring system (Figure 4) is only appropriate for patients with an underlying disorder that can be associated with DIC. The scoring is done based on the thrombocyte count, Fibrin split products, D-Dimer, prolonged aPTT and fibrinogen levels. A score of 5 and higher is considered as overt DIC. The DIC scoring by ISTH can be used in cases both with and wihout underlying infectious[63]. Bakhtiari et al

Figure 4: *International Society of Thrombosis ve Hemostasis (ISTH) DIC Scoring System.*



reported the sensitivity of the ISTH DIC scoring system as 97% and specifity as 91%. The strong relationship betwen the scoring system and mortality has been demonstrated in a few studies. For every 1 point increase in the score, ghe mortality was noted to rise between 1/25 to 1/29[64].

TREATMENT

The main goal of the treatment in DIC is to correct the underlying obstetrical cause. Once the precipitating cuase is addressed DIC usually resolves. Besides, supportive treatment should be implemented to correct the coagulation disorder[36]. The following section comprises this part of the clincial management.

Replacement of Blood and Blood products

The decision for replacement of blood products is given after consideration of laboratory results and the clinical condition all toghether. In general, platelet suspensions are administered to patients with platelet counts less than 50×10^9 and actively bleeding. In patients without bleeding, platelet transfusion is limited to patient's with a platelet count with less than 30×10^9 dir[65]. There is no indication to transfuse coagulation factors and plasma if there is no active bleeding. However, if the active bleeding occurs is in the setting of prolonged PT and aPTT, then Fresh Frozen Plasma (FFP) should be administered at a dose of 10-20 ml/kg[65].Higher doses may be administered based on response noted during serial follow-up testing. If FFP's are not feasible due to concerns of fluids overload, non-activated prothrombin complex concentrate (PCC) may be administered at 25-30 U/kg dose[66]. Since this concentrate, contains only Vitamin K dependent factors it will replace the deficit partially. As it may worsen the severity of the dissesminated intravascular coagulation activated PCC should not be used, instead only non-activated PCC should be used[67].

In congenital isolated fibrinogen deficiencies with levels less then 1gm/L, cryoprecipitate or fibrinogen factor concentrates should be used. Since the fibrinogen consumption may be faster , fibrinogen concentrates should be administered for values above 1gm/L in DIC. 4 gm of fibrinogen concentrates, increase serum fibrinogen levels to 1gm/L[68]. In a study done on 30 patients with acquired hypofibrinogenemia, i.e. (<1.5g/lt), it was shown that the bleeding stopped without any further surgical or radiological intervention in 46% of the cases. In the same study, no adverse effects, including thromboembolic events related to the use fibrinogen concentrate were noted[69].

Management of the Massive Bleeding

Obstetrical bleedings are the most common reason of maternal mortality. In a healthy female, there may be no alterations in vital signs until 10-15% of the blood volume has been lost. Tachycardia is the first finding of bleeding. 30% of the blood volume may have been lost by the time that severe hypotension is noted[70]. Management of postpartum bleeding warrants medical, mechanical and surgical interventions requiring significant amount of blood and blood products[71].

In obstetrical bleedings, the replacement of blood and blood products should be similar to the approach to trauma patients[72]. Management of massive obstetrical bleeding is summarized in Table I. The purpose of management of bleeding is to maintain the patient normotensive, normothermic and ensure adequate replacement of clotting factors. First of all, two large bore peripheral IV lines should be placed. Initiation of crystalloid or colloid fluids remains a controversy because colloid solutions may affect coagulation[73]. Rapid transfusion of volume expanders may lead to dilution of coagulation factors. Therefore, blood replacement should be implemented as soon as possible. O Rh negative blood transfusion must be started emergently and typed & screened, cross matched blood should be prepared within maximum 45 minutes[65].

Table I: *Management of Massive obstetrical bleeding (Reference #65 is used in to build this figure).*

Erythrocyte suspensions
- Firstly, use O Rh (-) erythrocyte suspensions (ES)
- Cross matched ABO and Rh compatible blood should be available within maximum of 45 min
- Maintain circulating blood volume with ES as needed
- Avoid hypothermia (use blood warmers)

Fresh frozen plasma
- Transfuse one unit of plasma to every one unit of ES
- PT & APTT values should be less than 1.5 times normal

Platelet transfusion
- Transfuse one to two adult doses of platelets to every 8-10 units of ES
- Platelet count should be $>50 \times 10^9$/l

Fibrinogen
- Cryoprecipitate (dose = two donation pools)
- Fibrinogen concentrates (4 g)
- Fibrinogen level should be >1g/l

A study done by Hishberg et al showed that dilutional coagulopathy could be inevitable with more than 5units of blood tranfusion[74]. In another study done, use of 1:1 packed red blood cells and FFPs was demonstrated to decrease the mortality[75,76]. In another study, it was reported that prophylactic administration of thrombocytes decreased the need for other blood products in massive bleedings. Therefore, the need for 1-2 adult dosing thrombocyte replacement for every 8-10 units of blood is emphasized[77].

There is literature demonstrating that administration of cyroprecipitates and fibrinogens for fibrinogen levels less than 1.5gm/L decreaeses bleeding[78,79]. In a retropective study, the use of fibrinogen concentrates decreased the need for erythrocyte and thrombocyte suspesions, FFPs as well as led to a significant decrease in blood loss and improved coagulation factors. The reported study includees mainly obstetrical cases and suported the use of fibrinogen factor concentrates in placental abruption and placenta previa[78]. Serial measurement of whole blood count and coagulation parameters are essential in regards to whether to carrying on or hold further replacement of blood products. Caution should be given to prevent development of acidosis and hypothermia associated with transfusions. In massive transfusions, it has been shown that acidosis hinders the union of the coagulation complex and that hypothermia decreases thrombocyte activation[80]. In massive obstetrical bleeding followign steps should be ensured in order

1. The bleeding should be controlled with surgical and radiological methods.
2. The circulating blood volume should be replaced with fluids and blood products and
3. Factors like, hypothermia and acidosis triggering abnormal coagulation should be controlled. The management of blood products should be done as listed in Table I.

The role of activated Factor VII

The experience with the use recombinant Factor VIIa (rFVIIa) in massive obstetrical bleedings is increasing. Gabriel et al discovered that rFVIIa levels above physiological limits are directly activating Factor X located on the surface of activated platelets[81]. A study reviewing the Northern Europian Obstetric records, demonstarted that the bleeding was effectively controlled in 83% of patints who were treated with FVIIa[82]. In another prospective study, the use of rFVIIa in patients with postpartum bleeding was shown to prevent from postpartum hysterectomy by 91%[83].

However, yet there are questions regarding the use of rFVIIa which need to be answered. First of all, the dose to be used in massive obstetric bleedings has not been standardized, yet. Various groups used doses ranging from 15 mcg/kg to 120mcg/kg[65]. Secondarily, in cases with platelet counts above $100x10^9$ and less severe coagulopathies the response to rFVIIa is higher. This finding supports the replacement with blood products early on in the course to bring the response to rFVIIa to a more adequate level. Acidosis and low fibrinogen levels decrease the optimum response to rFVIIa[84]. As a pre-hemostatic agent, rFVIIa may theoretically lead to thromboembolic complications. Especially, in hypercoagulable states like pregancy this could become a problem of importance. In a recent review, only one out of 48 patients who who were treated with rFVIIa developed a thromboembolic complication[85]. Another reason is that the costs of rFVIIa treatment are high. However, if the surgical procedures and prolonged hospital stay including admission to the ICU are considered as well it may balance out.

Although, rFVIIa seems to be an effective treatment method in massive obstetrical bleedings there is need for further research in regards to optimum dosing, frequency and proper timing of use.

Pharmacological Treatment

The use of pharmacological agents inhibiting the coagulation and fibrinolytic systems in Disseminated Intravascular Coagulation is still controversial. Heparin will theoretically inhibit intravascular coagulation and subsequent fibrinolysis through inhibition of the thrombin activity.

Heparin is especially recommended in DIC cases associated with thrombosis without stigmata of bleeding. In patients considered for Heparin treatment, fractionated heparin should be the treatment of choice given its short half life and reversible actions and should be administered as continuous intravenous infusion at 10 μ/kg/hr. In these patients, the clinical response should be taken into account rather then the use aPTT in the monitorization of the anticoagulant effect[36]. The use of anti-fibrinolytic agents such as Tranexamic asit and ß-aminocaproic acid is in general contraindicated in DIC. However, these medications may be effective in life threatening bleedings[86].

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