Management of Disseminated intravascular coagulation during pregnancy

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Disclosure

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Agenda

• INTRODUCTION
• PREGNANCY COMPLICATIONS
• APPROACH TO THE PATIENT
• FOLLOW-UP LABORATORY TESTS and TRANSFUSION TARGETS
• SUMMARY AND RECOMMENDATIONS
Definition

- Primarily a thrombotic process
  - Systemic process producing both thrombosis and hemorrhage
  - Also called consumption coagulopathy and defibrination syndrome
  - Its clinical manifestation may be widespread hemorrhage in acute, fulminant cases
INTRODUCTION

• Pathologic disruption of the finely-balanced process of hemostasis.
• Massive activation of the clotting cascade results in widespread thrombosis.
• The end result is multiorgan failure and hemorrhage.
• 1 to 5 percent of all cases of DIC in high-resource countries; the frequency is higher in low-resource countries.
• Any patient in DIC presents a major management challenge, and this challenge is further complicated when a viable fetus is also present.
PREGNANCY COMPLICATIONS THAT MAY LEAD TO DIC

• Abruptio placentae
• Severe preeclampsia, eclampsia, or HELLP syndrome
• Amniotic fluid embolism
• Acute fatty liver of pregnancy
• Dead fetus syndrome
• Septic abortion
• Massive hemorrhage, which may be a consequence of disorders such as placenta previa, uterine rupture, placenta accreta, or postpartum uterine atony
Pathophysiology of the clinical manifestations of disseminated intravascular coagulation

Intravascular activation of coagulation

Consumption of clotting factors and platelets

Fibrin deposition in microcirculation

Secondary fibrinolysis

Generation of fibrin-degradation products

Microangiopathic hemolytic anemia

Ischemic organ damage

Bleeding diathesis

Thrombotic manifestations
Excess Thrombin in DIC

- **Coagulation consumption**
- **Anticoagulant**
- **Bleeding**
- **Thrombosis**
- **Fibrinolysis**
- **Antifibrinolysis**
- **Platelet dysfunction**
- **Platelet aggregation**
- **Platelets**
CLINICAL MANIFESTATIONS

- Bleeding
- Shock
- Dyspnea, hemoptysis
- Acute renal failure
DIAGNOSIS

• Typical clinical features
• Laboratory findings of coagulopathy
• Scoring System
  – Scoring systems are not necessary for diagnosis of DIC
<table>
<thead>
<tr>
<th>Clinical condition predisposing to DIC</th>
<th>ISTH Criteria</th>
<th>JMWH Criteria</th>
<th>JAAM Criteria</th>
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<td>SIRS score $\geq 3$—1 point</td>
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<td>50–80—2 points</td>
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<td>FDP ($\mu g/ml$)</td>
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<td>Adequate type of DIC</td>
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<td>FO, BL, MB</td>
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<tr>
<td>PPIC</td>
<td>Elevation</td>
<td>BL, MB</td>
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Excess thrombin generation
- *Increased thrombin–antithrombin complexes*
- *Increased fibrinopeptides*
- *Increased prothrombin fragments 1 and 2*
Decreased protein C and protein S and antithrombin
Increased fibrinolysis
- *Increase in plasmin*
- *Decreased plasminogen levels*
- *Decrease in α2-antiplasmin*
- *Increase in plasmin–antiplasmin complexes*
- *High levels of plasminogen activator inhibitors*
Newer markers (signifying thrombosis–inflammation cross-link)
- Increased soluble thrombomodulin
- Increased amount of histones and extracellular deoxyribonucleic acid
- Increased high-mobility group box protein-1
- Neutrophil activation in the form of neutrophil extracellular traps
- Decreased ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13)
- Complement markers (C3, membrane attack complex, and mannose-binding lectin)
- Presepsin (soluble cluster of differentiation 14 subtype)
APPRAOCH TO THE PATIENT

• The key elements in managing the pregnant woman with DIC are to identify and treat the underlying disorder and provide supportive care, particularly replacement of blood products.
Initial steps

• Initial considerations in evaluation and management of the undelivered gravida in DIC
Treatment

• The cornerstone of the treatment of DIC is treatment of the underlying condition (Grade C, Level IV).
MANAGEMENT

• Notify the anesthesia service
  • Notify the anesthesia staff for assistance with patient management and to provide anesthetic support for delivery.
  • Epidural and spinal anesthesia are generally contraindicated in patients with a severe bleeding diathesis because of risk of epidural hematoma.
MANAGEMENT

• Establish intravenous access and begin fluid resuscitation
  • Establish intravenous access peripherally with at least two large bore (16 gauge or larger) catheters and infuse crystalloid to support blood pressure (systolic ≥90 mmHg) and maintain urine output (at least 0.5 mL/kg/hour).
  • The best approach to fluid resuscitation remains controversial.
  • A common formula is 3 liters isotonic saline per 1 liter estimated blood loss ("three to one rule").
MANAGEMENT

- Notify the blood bank and initiate transfusion therapy
  - Transfusion for treatment of DIC is appropriate in obstetrical patients since they have or are at high risk for serious bleeding or are likely to require an invasive procedure.
  - Notify the blood bank of the potential need for massive transfusion and initiate a massive transfusion protocol, if available.
MANAGEMENT

• Type and cross match a minimum of 6 units packed red blood cells, 6 units fresh frozen plasma, 10 bags of cryoprecipitate, and 1 six-pack of platelets.
  • In most instances, preparation of fully typed and cross-matched blood requires at least 20 minutes.
  • Clinicians can begin transfusion immediately using type O Rh(D)-negative pRBCs, if necessary, and then switch to type-specific or typed and cross matched pRBCs when available.
  • Uncross-matched fresh frozen plasma is type AB (either Rh positive or negative) and can be used when transfusion is necessary prior to obtaining crossed-matched fresh frozen plasma.
Massive Transfusion

- Many massive transfusion protocols recommend transfusion of red blood cells, fresh frozen plasma, and platelets in a ratio of 1:1:1 (termed hemostatic resuscitation).
- Note that 1 unit of apheresis platelets is equivalent to 6 units of non-apheresis (ie, random donor or whole-blood derived) platelets.
- A one to one ratio of packed red blood cells to fresh frozen plasma has been associated with higher survival in trauma patients than higher ratios (ie, more packed red blood cells than fresh frozen plasma).
TRANSFUSION

• Replacement with FFP is indicated (1 unit of FFP increases most coagulation factors by 3%)
• The replacement of 10 U of cryoprecipitate for every 2–3 U of FFP is sufficient to correct the homeostasis
• Platelet conc. at a dose of 1–2 U/10 kg body weight are sufficient for most DIC pt with severe thrombocytopenia.
Heparin

• During removal of a dead fetus
• Continuous i.v infusion in a dose of (5-10 unit/kg/hr).
FIBRINOGEN

• It is important to correct abnormally low fibrinogen levels, which commonly occur in obstetrical patients with massive bleeding.
• Cryoprecipitate, a source of concentrated fibrinogen, can take up to 45 minutes to thaw and become available for transfusion.
• Clinicians need to order cryoprecipitate with enough advance planning to allow for the thawing time.
• A fibrinogen concentration below 100 mg/dL is generally treated with 10 units of cryoprecipitate (each unit of cryoprecipitate comes from one unit of whole blood, and raises the fibrinogen level by about 5 mg/dL).
• The usually administered dose of 4 g fibrinogen concentrate raises plasma levels by around 1 g/L.
The use of antifibrinolytic drugs, or tranexamic acid

- Prevent fibrin degradation by plasmin may reduce bleeding episodes in pt with DIC and confirmed hyperfibrinolysis.
- Drugs can increase the risk of thrombosis, and concomitant use of heparin is indicated.
Activated Protein C

- Antithrombotic effect
- Inhibits Factors Va and VIIIa.
- Indirect profibrinolytic activity through its ability to inhibit plasminogen activator inhibitor-1 (PAI-1)
- Limits generation of activated thrombin-activatable-fibrinolysis-inhibitor
**Clotting Factors**

- Clotting factor concentrates are not recommended for control of bleeding in DIC because of the limited efficacy afforded by replacement of single factors (FVIII or FIX concentrates), and the high risk of products containing traces of aPCCs that further aggravate the disease.

- If FFP transfusion is not possible due to fluid overload, prothrombin complex concentrate (PCC) (25–30 U/kg)) may be tried.
OTHER

• **Maintain oxygenation**
  - Keep arterial oxygen saturation above 95 percent.

• **Avoid hypothermia**
  - The patient should be kept warm with warmed blankets and other interventions (e.g., Bair Hugger forced-air warming system), as needed.
  - If large volumes of fluid and blood products are given, the infused fluids/blood products should be warmed so they are close to body temperature to prevent a significant drop in maternal core temperature.
OTHER

• Identify and address the triggering event
  • The cornerstone of therapy is to identify the underlying disorder leading to DIC and initiate appropriate treatment for that disease
    • Sepsis
    • Septic abortion
    • Fetal demise
    • Amniotic fluid embolism
    • Abruptio placentae
    • Acute fatty liver
    • Hemorrhage
LAB

• Order laboratory tests
  • Baseline panel consisting of a complete blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, fibrinogen level, and a fibrin-related degradation marker (eg, D-dimer)

• Appropriate cultures
  • Blood, urine, amniotic fluid
Lee and White test

• Prior to the return of the first set of laboratory studies, a red top tube (ie, no additives) containing 5 mL blood can be observed for clotting.

• At room temperature, if the blood in the tube clots within 8 to 10 minutes and the clot remains intact, the patient likely has adequate fibrinogen stores.

• If the blood in the tube does not clot or an initial clot dissolves, it is likely that the patient is markedly deficient in key clotting factors.
Follow-up laboratory tests and transfusion targets

- We draw laboratory studies initially every 30 minutes to guide blood product replacement, and we transfuse blood products to achieve the following minimum levels for delivery.
  - Platelet count $\geq 50,000$/microL
  - Fibrinogen $\geq 100$ mg/dL
  - Prothrombin (PT) and activated partial thromboplastin time (aPTT) less than 1.5 times control

As the clinical situation is stabilized, laboratory studies are obtained less frequently.
The optimal hemoglobin concentration for pregnant women who are about to likely depends on:

- Expected blood loss during delivery
- Baseline hemoglobin level and rate of fall
- Presence of medical comorbidities

The overall risk of mortality increases as the hemoglobin concentration decreases

- Minimum hemoglobin of 7 g/dL for nonpregnant individuals undergoing surgical procedures associated with significant bleeding and for patients receiving massive transfusions
FACT

• Perioperative red cell transfusion concluded that cardiac output does not significantly decline until the hemoglobin concentration decreases to 7 g/dL.

• Hematocrit target of 25 to 30 percent for initiating blood transfusion therapy because pregnant women with DIC have ongoing blood loss, which will further increase at the time of delivery, and because equilibration generally results in a fall in hematocrit.

• A lower hematocrit level is acceptable after the patient has delivered, is no longer actively bleeding, and is hemodynamically stable.

• A fibrinogen level ≥100 mg/dL is considered the minimum level necessary for adequate coagulation, but >200 mg/dL is better.
Indication of the use of rFVIIa

Indication

a. Active bleeding following administration of 6 to 8 units of red blood cells, 6 to 8 units of plasma, and one dose of platelets
b. Administer 10 units of cryoprecipitate if the fibrinogen is <100 mg/dL

Contraindications

a. pH < 7.00
b. Immediately following cardiac arrest
c. Patient considered "unsalvageable" by staff surgeon
d. Recent thrombotic event, MI, or stroke

Dosing of rFVIIa

45-60 micrograms/kg as a half dose and repeat this dose in 30 to 60 minutes

Always round down to the nearest full vial for doses of rFVIIa
SUMMARY AND RECOMMENDATIONS

• Obstetrical disorders that may initiate disseminated intravascular coagulation (DIC) include abruptio placentae, severe hemorrhage, HELLP syndrome/eclampsia/severe preeclampsia, amniotic fluid embolism, acute fatty liver of pregnancy, septic abortion, and dead fetus syndrome.

• Placental disorders can cause DIC because trophoblast cells strongly express tissue factor, which is important in the production of thrombin.

• Uncontrolled production of thrombin results in widespread intravascular fibrin deposition, widespread fibrinolysis, and hemorrhage, with further depletion of coagulation factors.
SUMMARY AND RECOMMENDATIONS

• The diagnosis of DIC is based on the presence of typical clinical features (bleeding, shock, respiratory distress, renal failure) supported by laboratory findings of coagulopathy.

• The key elements in managing the pregnant woman with DIC are to identify and treat the underlying disorder and provide supportive care, particularly replacement of blood products.

• The initial steps in evaluation and support of the pregnant woman in DIC are: inform the blood bank, anesthesia, and pediatric services; insert two large bore intravenous catheters; keep oxygen saturation >95 percent; identify and eliminate the triggering event; monitor vital signs and blood loss; and avoid hypothermia.
SUMMARY AND RECOMMENDATIONS

• We type and cross match a minimum of 6 units packed red blood cells, 6 units fresh frozen plasma, 10 bags of cryoprecipitate and 1 six-pack of platelets, and begin transfusion of blood products prior to getting initial laboratory results back. We suggest transfusion of red blood cells, fresh frozen plasma and platelets in a ratio of 1:1:1 in cases of severe DIC.

• The key points in obstetrical evaluation are review of the prenatal record, with particular attention to risk factors for DIC and comorbidities with potentially severe sequelae from DIC (eg, placenta previa); establishment of gestational age, determining whether fetal or placental abnormalities are present; and assessment of the fetal heart rate pattern and uterine contractions.

• We draw laboratory studies every 30 minutes to guide blood product replacement, and we transfuse blood products to achieve the following minimum levels for delivery.
  
  • Platelet count ≥50,000/microL
  • Fibrinogen ≥100 mg/dL
  • Prothrombin (PT) and partial thromboplastin time (PTT) less than 1.5 times control
  • Hematocrit 25 to 30 percent
SUMMARY AND RECOMMENDATIONS

- It is desirable, but not always possible, to correct the bleeding diathesis prior to surgery. If a cesarean has to be performed urgently, then packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate should be available in the operating room and administered if there is clinical or laboratory evidence of impaired coagulation.

- Uterine bleeding that persists despite standard measures, we suggest using a Penrose drain or urinary catheter as a uterine tourniquet. This procedure markedly reduces blood loss and allows time for the anesthesia team members to catch up with transfusion requirements.
Treatment summary

1. Control bleeding using surgical and/or radiological interventions
2. Aim to try and restore circulating blood volume using fluids and blood products
3. Control exacerbating factors for abnormal coagulation especially, hypothermia and acidosis
4. Blood product support as follows

Red cells
- Use O negative red cells first
If no record of red cell antibodies, ABO and Rh compatible, cross matched blood should be available within 30 min (maximum of 45 min)
Replace red cells as required to maintain circulating blood volume
Use blood warmer to avoid hypothermia

Fresh frozen plasma
- Transfuse one unit of plasma to every one unit of red cell
Aim for PT & APTT less than 1.5 times normal (normal for PT ~15 s and APTT ~35 s)

Platelet transfusion
- One to two adult doses after 1.5–2 blood volume replacement (equivalent to 8–10 bags of red cells)
Aim for a platelet count over $50 \times 10^9$/l

Fibrinogen
- Cryoprecipitate (dose = two donation pools)
Fibrinogen concentrates (4 g)
Aim for fibrinogen level over 1 g/L
Fig. 1: Algorithm summarizing diagnosis and management of DIC during pregnancy.
THANK YOU

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Learn as if you were to live forever