PRESENT THERAPEUTIC ATTITUDE IN BLOOD COAGULATION DISORDERS GENERATED BY SEPTIC-OBSTETRICAL CONDITIONS

Introduction

Obstetrical and gynecological hemorrhage frequently generates a multitude of clinical complications, raising problems related to their etiopathogeny and especially therapy, always representing an extreme emergency.

From the wide range of obstetrical hemorrhages, special attention should be paid to hemorrhages caused by the disorder/disturbance of the fluid-coagulant balance, these being the most fearful ones due to the particular risk, dramatic character and extremely difficult therapy.

The disseminated intravascular coagulation syndrome (DIC) is the main cause of the coagulation disorders generated by the severe septic conditions and obstetrical septic shock.

DIC is defined as an acquired pathological deviation of the hemostasis mechanisms, characterized by the intravascular initialization of a diffuse acute blood coagulation process, which mainly affects the microcirculation, by obstruction, affecting the peripheral irrigation (O2 supply) and inducing metabolic cell suffrance. DIC is an extremely severe element (13). The syndrome is clinically manifested by diffuse hemorrhage due to the consumption of various coagulation factors and by multiple organic dysfunctions (MODS) following the disseminated micro-thromboses.

DIC is not a pathogenical mechanism that is specific to sepsis, but might also occur in other obstetrical pathological conditions or medical and surgical aggressions.

The obstetrical infections that can develop a systemic inflammatory reaction (SIRS) – sepsis – septic shock – DIC are as follows:

- Pathological conditions in obstetrics
  - Complicated abortion
  - Septic complications of the therapeutic or on request abortion
  - Intra-uterus infection (corioamniotitis)
  - Puerperal infections: metritis, uterus gangrene, septic thromboflebitis, ovaritis, salpingitis,

Summary:

This paper presents information regarding the pathogenesis and the DIC syndrome treatment in the severe septic conditions and septic – obstetrical shock. The modifications of the hemostasis during normal pregnancy – hyper-coagulation associated with hypo-fibrinolysis create favorable conditions for the rapid development of DIC.

We have enumerated the triggering factors for DIC, emphasizing the importance of the extrinsic pathways for the activation of the clotting cascade.

The principles of DIC therapy have been presented: removal of DIC triggering factors, stopping the local and systemic inflammatory process, blockage of fibrinolysis, substitution of consumed clotting factors. It is considered that DIC treatment in the obstetrics field still remains a nowadays issue difficult to solve with major implications in maternal and perinatal mortality.

Keywords: blood coagulation disorders, septic-obstetrical conditions.

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pelviperitonitis, generalized peritonitis, septicemia, septicopioemia, septic shock
□ Septic pathology associated with gestation condition: urinary infections: pielonefritis, glomerulonefritis, acute appendicitis, acute colecystitis, peritonitis of other origin
□ Post C section infections, post catheter i-v infections
The changes of microcirculation and coagulolitic equilibrium during the normal pregnancy create favorable conditions for the rapid development of DIC.

The normal pregnancy is characterized by a hyper-coagulation status, a “thrombogen status” created by the increase of pro-coagulant factors, a selective decrease of certain circulating anti-coagulants within the conditions of fibrinolytic potential degradation.

The primary hemostasis suffers some specific disturbances. The increase of the progestative hormones concentration (mainly the progesterone) results in an endothelial hyperfunction increasing the PGI2 production, which is an inhibitor of the thrombocitary aggregation. Although the number of the platelets is within the normal limits, they start decreasing towards the end of the pregnancy. The high concentration of thrombomodulin and thromboxan A2, which have vasoconstrictor effect and generate platelet aggregation, support the hypothesis of a thrombocit chronic consumption in case of a slow intravascular coagulopathy (14).

In terms of coagulation: the concentration of the coagulation factors is increased for fibrinogen, f VII and VIII and smaller for f IX, X and XII.

Factors II, V, XIII are normal, while the factor XI is smaller. Prekalikrein and kininogen with a high molecular weight, and f XII and XI represent contact factors responsible for the first stage of endogen coagulation, are also higher.

As for the behavior of the coagulation inhibitors AT III and protein C (PC), they are not influenced in any way.

These modifications are associated with fibrinolyse modifications.

It has been noticed an increase of plasminogen concentration and α2 antiplasmin and plasminogen activators inhibitors, these ones being emphasized by the high concentration in the amniotic liquid and placenta. The result is the depression of the fibrinolyse.

The clotting-unclotting disequilibria during pregnancy are considered, within certain limits, a physiological phenomenon. The association of certain risk factors as shock or sepsis transforms the hyper-coagulation latent status into a clinical one, manifested by DIC or thrombosis accidents (11).

Pathogeny

DIC, the final consequence of a severe septic condition, generates a wide haemostatic disturbance, having an impact on all the stages of hemostasis: vascular plaquetary stage, coagulation, and fibrinolyse. The mechanism that releases the DIC is multiple (see figure1).

Table 1. Clotting modifications during pregnancy, during partum and post-partum (15)

<table>
<thead>
<tr>
<th>Mediating clotting factors</th>
<th>Pregnancy</th>
<th>Partum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>FI, VII, VIII, IX, X, XII, Prekalikrein KGNM, PAI2, FP₄, β thrombomodulin, Tromboxan A², Plasminogen, α₂ antiplasmin, PAI₁ and PAI₂</td>
<td>Fibrinopeptid A, D-dimers</td>
<td>F XIII</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D-dimers</td>
</tr>
<tr>
<td>Constant</td>
<td>II, V, XIII, Platelets, AT III Protein C</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Decreased</td>
<td>XI, Protein S</td>
<td>Platelets, PAI₁ and PAI₂</td>
<td>II, V</td>
</tr>
</tbody>
</table>

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Acute DIC is initiated in different ways:

1. The endothelial inflammatory reaction - is a phenomenon constantly present in infectious DIC. An increased number of macrophages and monocytes generate a large quantity of intercellular adhesion molecules (I.C.A.M.), vascular cell adhesion molecules (VCAM) and endothelial leukocyte adhesion molecules (ELAM) on their surface. At the level of slow blood flow microcirculation, they determine a strong adhesion of the polymorphonuclears (PMN) to the endothelial cells. The PMN are tightly connected with the endothelial cells and activated by endo-toxins and by the PAF, IL8, and fraction C5 and release important quantities of mediators: elastasis, catepsin, cytokines, acid radicals, which contribute to the activation and damage of endothelial cells. It denudes the collagenic skeleton of the capillary, which is a strong activator of f XII and the precalikrein, instantaneously causing the intrinsic intravascular coagulation.

2. Direct activation of coagulation

The endotoxins and TNF trigger the extrinsic coagulation activity by stimulating the tissue factor release – tissular thromboplastin by the affected endothelial and monocyte cells. The tissue factor fixes on f VIIa and the complex tissue factor + VIIa activates f X and IX. It has been proven that the extrinsic activation of the coagulation plays a much more important role in triggering the coagulation than the contact (intrinsic) activation.

3. Platelets activation

The platelets are activated directly by the endo-toxins and also by the complement cascade factors and the plaquetary activating factor (PAF). The plaquetary hyper-activation enables the installation of DIC and peripheral vasoconstriction (by elaboration of serotonin and thromboxane A2).

4. The role of coagulation inhibitors

It has been noticed a deficit of coagulation inhibitors: antithrombin (AT III), C protein system, protein S, tissular factor pathway inhibiting system (TFPIS), and thrombomodulin. Therefore, it appears a pro-coagulant status.
The **Fibrinolyse** by the activation of the plasminogen into plasmin is a reactive mechanism, which is beneficial at the very beginning.

The endotoxins, TNF enable the release of tissular activator of plasminogen from endotels and monocytes. They activate the plasminogen into plasmin.

The plasmin has a thrombotic effect, in excess degrading the circulating fibrinogen and the fibrine. The degradation products of fibrinogen also inhibit platelets function, the action of thrombin, factors V, VIII, and XII and the first component of the complement.

**Dynamics of pathological phenomena in DIC**

As the DIC is an evolutonal process and has three stages:

- **Stage 1** of compensated hyper-clotting, clinically rather short, only the lab exams may help detect the instauration of the hyper-clotting status – moderated increased platelets.

- **Stage II** of decompensated hyperactivation, which clinically is characterized by multiple organic dysfunctions is due to the disseminated microthromboses and by a hemorraghic diathesis of consumption coagulopathy. Biologically: it appears an abrupt decrease of the coagulation parameters (platelets <, Fg<, TQ elongated), low coagulation inhibitors, increased fibrine monomers, normal euglobulinic clot formation time (ECFT), FDP within the normal limits.

- **Stage III** – of excessive activation of fibrinolyse process, where the multi-organic insufficiencies are obvious, the hemorrhage is severe, the blood being unable to coagulate. Biologically: TLCE much <, the test F.D.P (fibrine degradation products) intensive positive D-dimeris. The coagulogram in DIC should be repeated every 4 hours, the DIC being a rapid evolitional process.

**Treatment**

The treatment of DIC syndrome of obstetrical septic conditions is difficult and complex, without a sure remedy for the DIC affected persons.

Therapeutic principles:

- **elimination of DIC triggering factors** – etiological treatment
- **blockage of local and systemic inflammatory process LSIP**
- **blockage of fibrinoformation and constituted thrombus formation**
- **Substitution of consumed factors**

**Elimination of DIC triggering factors**

The causes that trigger the DIC are infection and sepsis. Without proper cause-related treatment, any therapy initiated will be resultless.

The infection must be treated with wide specter antibiotics and after the identification of the pathogen germs, with focused antibiotic therapy.

The septic source will be surgically drained by exeresis, drainage, and lavage. Tissue level injuries must be avoided during obstetrical surgical interventions, the uterus, and placenta representing major thrombo-plastic discharge sources (9).

The endotoxin might be eliminated by plasmapherese and neutralized by immunological therapy: antiendotoxin antibody, natural polyclonals, antimiiese endotixi nic monoclonal antibody, and antagonistic competitive lipopolizaharidics on receptors. These new therapeutic acquisitions are under assessment and represent valuable therapeutic perspectives for the future.

**Blockage of local and systemic inflammatory process (LSIP)**

It can be realized by prevention of major hemodynamic, metabolic, fluid-coagulant disequilibria that can degenerate into shock and DIC.

The necessary treatment consists of a fast hemodynamic rebalance, correct oxygenation, acid-basic balance, and anemia correction. Thus, this will avoid the local effects of hypoxia, vascular endothelium damage, and the release of inflammation mediators, which interfere with the clotting cascade, and the production of systemic inflammatory reaction syndrome (SIRS).

**Blockage of fibrinoformation and constituted thrombus formation**

Intravascular thrombin generation is the pathogenic mechanism essential in DIC. By the inhibition of thrombin activity, the fibrinoformation can be blocked and, therefore, hyper-coagulation prevented.

Heparin was considered first class treatment in DIC, at present the heparin-therapy being selective. Heparin, without being an anti-coagulant, by combination with AT III coagulation physiological inhibitor, accelerates and intensifies the activity of the latter. Usually, AT III inactivates slowly and progressively the excess thrombin, after the specific action upon the fibrinogen. The reaction between AT III and thrombin is instantaneously produced after fixation of heparin on AT III.

AT III is consumed consecutively to the process. Besides thrombin, AT III also inhibits f X a, f VII a, IX a, XII a, XIII a, plasmin and kalikrein. Therefore, it is determined
that AT III has a central role in adjustment of hemostasis and the activity of heparin is connected directly to the AT III quantity.

It was confirmed the efficiency of heparin early administered in very small doses (100-200 UI/kg/c24h) within the initial stages of the DIC, when there is hyper-coagulation and thrombosis tendency. Heparin is inefficient in DIC with hemorrhagic clinic manifestations, where the coagulation factors were consumed and there is AT III deficit.

The use of heparin in small doses can be done only after the correction of AT III and coagulation factors (4).

Substitution of consumed factors

Decreased essential coagulation factors in DIC: f V, VII, VIII fibrinogen, platelets, AT III should be rapidly replaced, even faster than their consumption in the thrombosis process (see table 2).

The substitution can be done by:

- Fresh frozen plasma – contains, at an optimum ratio, coagulation factors II, V, VII, VIII, X, XI in inactive status and in adequate hemostatic concentration and also coagulation inhibitors -AT III is the most important inhibitor of the coagulation system (see table 2). Potential risk: transmission of viral infections.
- Plasmatic cryoprecipitate appreciated for the high content of fibrinogen 200-300 mg/package is reserved to hypofibrinogemy forms. The cryoprecipitate also contains f VIII, XIII, fibronectin.
- Fresh integral blood is necessary to maintain volenmy, correct Ht at values above 30% and supply of coagulation factors and platelets. Factor V (labile) and platelets can be found only in fresh blood. The fibrinogen concentration from preserved blood is 0.5-0.7 g/500ml. Liofilisated plasma contains 0.7g/200ml.
- Platelets concentrates are recommended for hemorrhage with hazardous thrombocytopenia (platelets decreased to 20,000/mm3). Platelets level of 50,000/mm3 generally offers haemostatic security.
- Coagulation factors concentrates
  - Human fibrinogen. It is aimed to obtain and maintain a fibrinogen concentration in plasma of over 50mg %. Recommended doses are 2-12-24 g/day. Initial doses 2g in 30 min. Repeated every 3 hours.
  - Factor VIIa recombined - Novoseven – amplifies thrombin generation on extrinsic pathway of coagulation only at vascular damage spot by formation of a complex with X tissue factor. Coagulation systemic activation is not produced.

Posology: recommended doses 4.5 KUI (90mg/Kgc intravenous in bolus). The following doses 3-6 KUI (60-120 mg/Kgc) every 2h until the clinic amelioration.

- Concentrate of AT III In infectious DIC there is a precocious and intense constant diminution of AT III activity. Besides the alteration of the hepatic synthesis, the AT III deficit reaches 20-40% (N=80-120%) and the bisection time decreases from 60h to 4h. Therefore, the pluri-quotidian monitoring of the AT III level is necessary.

The data presented justify the precocious treatment with AT III. The AT III supply can be realized by perfusion of fresh plasma, cryoprecipitate, or fresh blood. There is also AT III concentrate. In an acute DIC, the daily AT III dose needed is 100UI/Kgc. Identical or smaller doses should be administrated daily until disappearance of clinical or biological signs of DIC.

The instituted treatment should be associated with AT III treatment, the optimum administration order being AT III followed by prothrombinic complex concentrate and then.

As regards the effectiveness of AT III administration in severe sepsis, there are different opinions. Some authors evaluates favorably the AT III effect, others consider that AT III has not succeeded to prove an improvement of evolution and of mortality rate in DIC. Administered together with heparin it increases the hemorrhage risk.

- Activated C Protein (DROTRECOCIN ALFA ACTIVATED) is another inhibitor of coagulation indicated in DIC for its anti-thrombotic, anti-inflammatory and profibrinolytic properties (15).

Synthesized in liver in the presence of vitamin K, C protein is activated under the action of fII situated in a complex with thrombomolulin. Thus activated it acquires the capacity of inactivating 2 major coagulation factors f Va and f VIIIa, stopping the clotting cascade.

The reduction of APC thrombin generation can prevent the thrombin proinflammatory effects:

- activation, adhesion and platelets aggregation
- release of vasoactiv and proinflammatory substances.
As regards the treatment with Drotrecogin alfa activated in DIC infectiously induced, numerous studies appreciate a favorable effectiveness of the treatment. APC has produced amelioration of organic dysfunctions present in severe sepsis and has significantly reduced the mortality rate. The only potential adverse reactions are controlled bleeding resulting from surgical interventions.

Fibrinolyse inhibitors

The introduction without prior consideration of the antifibrinolytics in DIC therapy would be an error, if it were to consider the positive effect of the secondary fibrinolysese for the maintenance of tissular perfusion in case of excessive intravascular coagulation. The antifibrinolytic treatment must be applied only in case of severe hemorrhage, where reactive hyperfibrinolysis was confirmed.

Aprotinin (trasylol) is preferred to synthetic fibrinolytic inhibitors (EAC, tranexamic acid) as it inhibits not only plasmin and plasminogen activators, but also other proteolitic enzymes: kalikrein, tripsin, and elastasis.

Administration schedule: initial dose 500,000 UKI in vane and then 200,000 UKI every 4-6 h.

Aminocaproic acid EAC inhibit the plasminogen activators. Doses used: 4-6 g i-v initial dose then perfusion with 1-1, 5 g/h without exceeding 30g/day.

Mortality rate by DIC is 26-85%.

The difficulty of DIC is given by the hemorrhagic disorders installed occurring in parallel with multiple organic dysfunctions difficult to correct and in obstetrics, it is associated with triggering obstetrical entities that should be promptly recognized and solved.

DIC treatment in obstetrics remains a difficult present problem to solve with major implications in maternal mortality.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Critical values</th>
<th>DIC without hemorrhagic manifestations and IRA</th>
<th>DIC without severe hemorrhage</th>
<th>DIC with severe bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen fresh plasma</td>
<td>5-10 ml/kg/h</td>
<td>5-10 ml/kg/h</td>
<td>+/- based on the shock type</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>100-200 u/Kg/24h continuous perfusion</td>
<td>± based on shock type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>10-50x 109/l</td>
<td>&lt;20x109/l 0.1 u/Kg</td>
<td>&lt;50x109/l 0.1 u/Kg</td>
<td></td>
</tr>
<tr>
<td>PPSB</td>
<td>Thromboplastin time &lt;20-40%</td>
<td>&lt;20% 50ui/Kgc</td>
<td>&lt;40% 20-40ui/Kg</td>
<td></td>
</tr>
<tr>
<td>F VII</td>
<td>4.5 KUI/Kgc</td>
<td>4.5 KUI/Kgc</td>
<td>4.5 KUI/Kgc</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>&lt;50mg%</td>
<td>50mg/Kgc</td>
<td>50mg/Kg</td>
<td></td>
</tr>
<tr>
<td>AT III</td>
<td>&lt;70%</td>
<td>70-100ui/Kgc</td>
<td>70-100ui/Kgc</td>
<td></td>
</tr>
<tr>
<td>C Protein</td>
<td>24 mg/Kgc/h</td>
<td></td>
<td></td>
<td>500,000 u UKI/Kgc/h</td>
</tr>
<tr>
<td>Aprotinin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Therapeutic behavior in DIC (after Şerban and Schramm)
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