Use of recombinant human activated protein C in treatment of severe sepsis in a pregnant patient with fully symptomatic ovarian hyperstimulation syndrome

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Summary

Background: Severe sepsis during pregnancy is a life-threatening condition for the mother, due to multiorgan failure and uncontrolled inflammatory response. It is associated with high risk of death for the fetus.

Case Report: The paper presents the course and treatment of severe iatrogenic sepsis in a patient in very early pregnancy. The sepsis was a result of complications after overstimulation of the ovaries in the course of treatment of infertility. The risk of the patient’s death, assessed in the Intensive Care Unit according to APACHE II and SAPS II scores was 73%, whereas indirect assessment of the embryo in the 3rd week of pregnancy, based on determination of serum gestational hormone levels was ambiguous, but rather unfavorable. The patient’s condition improved considerably after intensive treatment, including, among others, the use of activated protein C (APC). After the completion of treatment, in the 5th week of pregnancy, the gestational hormone levels increased to the values appropriate for such fetal age. The development of pregnancy was also confirmed by ultrasonography.

Conclusions: The paper presents a case of severe sepsis in the course of ovarian hyperstimulation syndrome, not described in the literature so far, as well as the first successful administration of activated protein C in 21-day pregnancy.

key words: severe sepsis • ovarian hyperstimulation syndrome • recombinant human activated protein C (rhAPC)


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**Background**

Sepsis in pregnancy may have various etiology. Pregnancy causes numerous changes in the woman’s organism which may affect the quality of inflammatory response in the course of sepsis and increase the probability of septic shock. Severe sepsis is associated with multiorgan failure syndrome, which develops as a result of excessive or imbalanced response of the organism to an infection.

Ovarian hyperstimulation syndrome is a result of excessive reaction of iatrogenic etiology, caused by pharmacological induction of ovulation during the treatment of infertility. Severe sepsis coincident with ovarian hyperstimulation syndrome leads to disturbances of blood supply to, and function of many organs, together with coagulation abnormalities, and reduced blood supply to the uterus can cause fetal death, additionally worsening the patient’s condition and prognosis. Each of these disorders separately is life-threatening for the patient. The paper presents the first successful administration of activated protein C in a patient with severe sepsis in 21-day pregnancy.

**Case Report**

A female patient aged 31 was admitted to the ICU at the onset of septic shock. During the period immediately preceding the admission to the ICU she had been hospitalized in the gynecological ward, where she had been treated for ovarian hyperstimulation syndrome due to treatment of infertility and preparation of the patient for in vitro fertilization with subsequent embryo transfer.

On the 10th post-transfer day, the patient returned to the hospital because of malaise, faintness and ascites. Fully symptomatic ovarian hyperstimulation syndrome was diagnosed and symptomatic treatment with anticoagulation prophylactics enoxaparin sodium was instituted. The patient received FFP and albumin infusions and decompressing puncture of the peritoneal cavity was performed twice, resulting in evacuation of the total of 3000 ml exudate from the peritoneal cavity. On the 21st post-transfer day, the patient’s temperature increased to 38°C, with progressive faintness, dyspnea and vision disturbances. Physical examination revealed disturbances of consciousness in the form of confusion and hallucinations, progressive vision disturbances, hypotension 60/40 mmHg, tachycardia 170/min, dyspnea and anuria. After fluid resuscitation, dopamine infusion and administration of furosemide, scanty diuresis was obtained. Material for microbiological investigation was collected (blood, sputum and urine), with subsequent institution of antibiotic therapy (ciprofloxacin). Because of dyspnea aggravation (PaO₂ decrease to 40 mmHg, pleural exudate in clinical examination and on chest X-ray), circulatory failure and renal dysfunction, the patient was transferred to the intensive care unit where she was intubated. On intubation, the presence of purulent discharge in the airways was observed. The bronchial secretion was taken for cultures. The patient required ventilation with 100% oxygen, the use of catecholamines and diuresis forced with high furosemide doses. Chest auscultation revealed disseminated rales over the pulmonary fields as well as systolic murmur over the heart. Transthoracic echocardiography did not reveal impaired myocardial contractility, valve defects or exudate in the pericardial sac.

Examination of the abdomen revealed tenderness, weak muscle guarding and no bowel sounds. Ultrasonography, transabdominal and with a vaginal probe, did not reveal the presence of any abscesses in the ovaries and abdominal cavity. On the other hand, the examinations confirmed the presence of a blastula in the uterus and fluid in the peritoneal cavity. Complete hemodynamic monitoring (invasive measurements of cardiac output, systemic and pulmonary pressures), monitoring of ventilation parameters (airway pressure, lung compliance and capnometry), diuresis and metabolism was started. Empirical antibiotic therapy was extended by instituting carbapenem meropenem. The patient was sedated by i.v. diprivan infusion and received treatment supporting the impaired function of organs. Initially, she required ventilation with FiO₂=1.0 and cardiovascular function assistance with epinephrine, norepinephrine and dobutamine infusion. Diuresis was promoted by administration of fractionated furosemide doses. The treatment with plasma preparations and albumins was also continued.

After the initial compensating treatment and stabilization of the patient’s general condition, the case was consulted with the following specialists (Table 1).

The patient was diagnosed with severe sepsis, developed in the course of ovarian hyperstimulation syndrome (Table 2). Staphylococcal etiology was suspected.

The dynamics of sepsis progression, low efficacy of standard therapy and high risk of the patient’s death was considered to necessitate a quick decision concerning the additional use of recombinant human activated protein C (rhAPC) in the therapy.

Before the institution of the drug, the indications for, and benefits of the therapy, as well as the risks associated with the use of activated protein C, were analyzed thoroughly (Table 3).

The patient required the dose of 138.2 mg rhAPC administered as i.v. infusion over 96 h. According to the manufacturer’s instructions, the drug was infused at 24 mcg/kg/h rate.

On the second day of activated protein C infusion, the patient’s general condition improved significantly. The fever subsided, the leukocytosis and CRP level in the serum decreased (Figure 1). Blood cultures confirmed Staphylococcus aureus infection. The strain was sensitive to chinolones.

Hemodynamic parameters were assessed by measurements and calculations obtained from pulmonary artery catheter, and noninvasively from esophageal Doppler electrode first and later from Echocardiography (Figure 2).

Stabilization of the cardiovascular system allowing to discontinue epinephrine and norepinephrine infusion was obtained. Persistent systolic murmur over the mitral valve was still detectable on auscultation.

Sedation was discontinued and oxygen supply in the gas mixture reduced, the ventilation mode was changed to spontaneous respiration with PS and PEEP, and on the subsequent day assisted ventilation was stopped. The values of PaO₂/FiO₂ ratio were improved during the treatment (Figure 3).
Gradual increase of serum platelet count with simultaneous decrease of D-dimer level was observed (Figure 4). During the first 24 h of rhAPC therapy, efficient diuresis was restored. Normalization of renal parameters and elevated hepatic enzyme levels was obtained on the second and third infusion day. After discontinuation of sedative infusion, sedation and complete awakening of the patient, she underwent neurological and ophthalmological examinations. Neurological evaluation revealed no consciousness disturbances or symptoms of central nervous system pathology – paresthesia, muscular dystonia, abnormal tendon reflexes or paralysis. During the first 24 h after awakening mild visual acuity disturbances were observed, which disappeared completely after the next two days. Blood microbiology did not demonstrate the presence of Staphylococcus aureus in any control sample, so antibiotic medication was discontinued on the 13th day of hospitalization.

Table 1. Specialist consultations.

<table>
<thead>
<tr>
<th>Specialist</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologist</td>
<td>The value of neurological examination doubtful because of diprivan sedation. No signs of paresis of the extremities, tendon reflexes normal, meningeal signs absent, cerebrospinal fluid sterile, normal fluid pattern in general examination.</td>
</tr>
<tr>
<td>Ophthalmologist</td>
<td>No abnormalities of the anterior portions of the eyeballs. The optic discs well-delineated, pale, course and diameter of blood vessels normal, the retina unaffected. The patient's acute blindness unlikely to be of central origin, e.g. as a result of sclerosis multiplex.</td>
</tr>
<tr>
<td>Radiologist</td>
<td>Enhanced left lung contour on X-ray (purulent discharge found in the airways on intubation allows to interpret the image abnormality as an inflammatory lesion). Transabdominal USG shows no signs of progressive ascites. Fluid of low density. No abscesses on the ovaries and abdominal organs. A blastula present in the uterine cavity.</td>
</tr>
<tr>
<td>Internal medicine specialist</td>
<td>Hyperkinetic circulation. Systolic murmur over the mitral valve. No echocardiographic evidence of inflammatory lesions on the valve leaflets. No fluid in the pericardial sac.</td>
</tr>
<tr>
<td>Surgeon</td>
<td>The abdominal wall soft, with slight muscle guarding, peristalsis present with no signs of impotency, peritoneal signs absent. No indications for surgical intervention.</td>
</tr>
<tr>
<td>Gynecologist</td>
<td>The vaginal portion hard, conical in shape, the cervical canal closed. The uterine body of normal size, slightly enlarged in ultrasound scan (performed using a vaginal probe). A blastula of 5–7 mm size present. Beta HCG (1888) level low as compared with gestational age. Qualitative assessment of pregnancy and prognosis concerning the embryo's development and survival rather unfavorable. The patient's condition indicates the necessity of further clinical observation.</td>
</tr>
<tr>
<td>Mikrobiologist</td>
<td>Growth of G+ cocci in tested blood.</td>
</tr>
</tbody>
</table>

Table 2. Severe sepsis identification chart.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Increased number of G+ cocci in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory response</td>
<td>Leukocytosis 18 k/μl, CRP 113.3 mg/dl, purulent discharge in the airways, interstitial changes in the left lung on X-ray</td>
</tr>
<tr>
<td>Signs of multiorgan failure</td>
<td>PaO₂/FiO₂ =40–130, assisted ventilation FiO₂ =1.0–0.7</td>
</tr>
<tr>
<td>- respiratory system</td>
<td>Tachycardia 160/min, hypotension 60/40 requiring supply of 3 catecholamines, metabolic acidosis, peripheral perfusion impairment – tendency to development of bedsores</td>
</tr>
<tr>
<td>- cardiovascular system</td>
<td>Oliguria, creatinine =2.4 mg/dl</td>
</tr>
<tr>
<td>- hematological system</td>
<td>Thrombocytopenia 60 k/μl, elevated D-dimers, INR &gt;1.2</td>
</tr>
<tr>
<td>- nervous system</td>
<td>Confusion, hallucinations, acute blindness</td>
</tr>
</tbody>
</table>

Table 3. Qualification for treatment with recombinant human activated protein. C

<table>
<thead>
<tr>
<th>Patient's data</th>
<th>Age</th>
<th>Gender</th>
<th>Height</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31</td>
<td>F</td>
<td>170 cm</td>
<td>60 kg</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>170</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td>Severe sepsis</td>
<td>High risk of the patient’s death</td>
<td>Low efficacy of standard therapy</td>
<td></td>
</tr>
<tr>
<td>Active hemorrhage</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;30 k/μl)</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of head trauma</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Surgery &lt;12 h</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Interventions with potential hemorrhage risk</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

Gradual increase of serum platelet count with simultaneous decrease of D-dimer level was observed (Figure 4).

During the first 24 h of rhAPC therapy, efficient diuresis was restored. Normalization of renal parameters and elevated hepatic enzyme levels was obtained on the second and third infusion day.

After discontinuation of sedative infusion, sedation and complete awakening of the patient, she underwent neurological and ophthalmological examinations. Neurological evaluation revealed no consciousness disturbances or symptoms of central nervous system pathology – paresthesia, muscular dystonia, abnormal tendon reflexes or paralysis. During the first 24 h after awakening mild visual acuity disturbances were observed, which disappeared completely after the next two days. Blood microbiology did not demonstrate the presence of Staphylococcus aureus in any control sample, so antibiotic medication was discontinued on the 13th day of hospitalization.
The development of pregnancy was monitored every day with ultrasound and hormone level investigations. Consecutive check-ups revealed the presence of transudate in the peritoneal cavity and of the blastula, growing gradually, in the uterus. On the 13th day of ICU treatment (35th day after embryo transfer) ultrasound scan performed with a vaginal probe detected the presence of fetal heart beat.

Starting from the 7th day, the patient was undergoing intensive rehabilitation. On the 15th day she was transferred to the obstetric ward. In the evening of the day preceding discharge from the ICU, the patient’s temperature rose to 38°C; the fever subsided after the administration of paracetamol.

**DISCUSSION**

Sepsis of varied etiology may develop during pregnancy. According to the WHO report, sepsis accounts for 15% deaths of pregnant patients on a global scale [1]. Severe sepsis involves multiorgan dysfunction syndrome, developing as a result of excessive or imbalanced systemic response to generalized infection [2].

Ovarian hyperstimulation syndrome is observed in the course of response to hormonal therapy; as a result of pharmacological hormonal induction during the first 5 days after embryo transfer [3]. Both sepsis and ovarian hyperstimulation syndrome impair perfusion of vital organs, leading to multiorgan dysfunction, coagulation disturbances and death of the fetus, aggravating the patient’s condition and worsening the prognosis [4–9]. Each of the above syndromes alone is a dynamic process associated with a considerable risk for the patient’s morbidity and mortality. The concurrence of the mentioned risks necessitates well-coordinated, quick and effective action.

In the reported case, it was necessary to determine in detail the pathophysiology and pathomechanism of the observed pathologic symptoms. The infection developed in
the organism previously treated with gonadotrophic hormone. Vascular changes in ovarian hyperstimulation syndrome cause increased vascular permeability and transudation of protein-rich fluid into the body cavities, reduce the capacity of the vascular bed and lead to impaired perfusion of vital organs due to hypovolemia and intravascular clotting. The progressive symptoms of respiratory failure and renal dysfunction observed in the patient were regarded as the sequels of hormonal hyperstimulation which delayed the diagnosis of developing sepsis.

The infection could have been caused both by Gram-positive and Gram-negative bacteria. A Staphylococcus aureus strain was grown in culture of blood samples collected from the patient.

The infection could have originated from four potential sources:
1. Ovarian abscess developed after puncture or as a result of puncture of the ovarian follicle performed to collect the material for in vitro fertilization. It cannot be excluded that the presence of a purulent ovarian cyst passed unnoticed when the patient was being prepared for in vitro fertilization, or that infection of the adnexes developed as a result of egg cell collection;
2. Iatrogenic infection as a result of peritoneal puncture. Such diagnosis was supported by the presence of peritoneal signs: increased tonus, tenderness on palpation, muscle guarding, lack of bowel sounds. The onset of fever was observed 7 days after the last puncture. The fever was accompanied by diarrhea and tenderness of the abdominal wall. Repeated surgical and gynecological consultations, as well as ultrasound scans of the abdominal and pelvic cavity excluded the presence of abscesses and peritonitis, thus negating the necessity of surgical intervention;
3. Blood-borne infection due to repeated transfusions of blood preparations. Such diagnosis might be supported by dynamic development of severe sepsis symptoms observed in the patient: rapid aggravation of respiratory failure, tachycardia, hypotension, anuria. In blood-borne infections, the symptoms of multiorgan dysfunction progress very rapidly. Bacteria present on the skin are the most common source of infection, whereas insufficiently disinfected puncture/injection site is the porta of entry. Blood-borne infections can also be caused by transfusion of infected blood products. The patient had received repeated plasma transfusions and albumin infusions because of hypoaalbuminemia in the course of ovarian hyperstimulation syndrome. The estimates concerning the incidence of infections caused by transfusions of blood products vary in different reports and range from 0.3% to 10%, whereas the mortality rate due to post-transfusion sepsis has been estimated by FDA at 17% [10,11].
4. Endocarditis. Endocarditis is reported in 17-34% of sepsis patients [12,13]. Physical examination on admission to the Intensive Care Unit revealed the presence of a systolic murmur. However, transthoracic echocardiography performed twice did not confirm the signs of bacterial endocarditis. Anamnesis findings concerning past endocarditis were unclear. Echocardiographic evaluation of the heart was difficult because of marked tachycardia.

The patient was in developing septic shock, with severe multiorgan dysfunction (Table 2). Parallel to the decisions concerning antibiotic therapy, symptomatic treatment and support of impaired organ function, indications and contraindications for treatment with recombinant human activated protein C were considered.

Activated protein C significantly improves the effectiveness of treatment in severe sepsis. It has been demonstrated in a multicenter clinical trial PROWESS, as well as in many published case reports [14,15].

The prognosis depends on the number of organs affected by dysfunction and on the extent of insufficiency. Thus, the time of intervention is very important because it has an indirect impact on the quality of systemic response to treatment, and, consequently, on treatment efficacy. The ultimate result of treatment of severe sepsis depends on multidirectional intensive management, careful monitoring and adequate actions adjusted to changing clinical situation [16,17].

One of the most serious complications of rhAPC therapy reported in the PROWESS study was increased frequency of hemorrhagic incidents in the treated group (8.2%) as compared to control. If the patient is to be subjected to a procedure posing the risk of hemorrhage, or to surgical intervention, during the therapy, the administration of activated drotrecogin alfa should be interrupted two hours before the planned procedure and resumed 2 h after a less invasive procedure or 12 h after surgery [18].

The decision to institute rhAPC therapy in the reported case had been preceded by numerous specialist consultations aimed at the determination of indications for surgical or gynecological interventions, in order to avoid the necessity of interrupting the therapy once it was instituted. The effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis was confirmed by the observations of the patient’s clinical condition and laboratory results. As early as on the second day of APC infusion, the patient’s general condition improved significantly. The signs of generalized inflammatory reaction subsided and the function of vital organs improved. On the subsequent days, neurological signs and vision disturbances normalized, and the development of the embryo in the uterine cavity was confirmed.

Both severe sepsis and ovarian hyperstimulation syndrome affect the function of vascular endothelium, blood coagulation and signs of generalized inflammatory response. Both syndromes are characterized by increased concentrations of the same cytokines [4–9]. Therefore, potential effectiveness of activated protein C in the treatment of ovarian hyperstimulation syndrome might be implicated, which can become the subject of further research.

The course of disease in the reported case confirms the necessity of thorough and active observation of the condition of such patients.

The staphylococcal strains cultured from the patient’s blood were sensitive to ciprofloxacin and this antibiotic appeared to be effective because the subsequent blood cultures showed no bacterial growth. Additionally, the fact
of transient vision disturbances observed during intensive therapy may suggest staphylococcal etiology – purulent obstruction of retinal blood vessels causing blindness has been described in staphylococcal sepsis [12]. However, it was impossible either to confirm or to exclude such diagnosis in the reported case.

The patient will require further follow-up for neurological symptoms and blindness. Her mother and brother suffer from sclerosis multiplex. The neurological symptoms observed in the patient were initially differentiated with this diagnosis.

CONCLUSIONS

1. The case report presents complex pathomechanism of multiorgan failure resulting from coincident symptoms of hormonal hyperstimulation and severe sepsis.

2. The resolution of symptoms of severe sepsis was achieved by timely, aggressive, goal directed, symptomatic and substitution therapy comprising blood products and drotrecogin alfa (activated).

3. The fact of saving the pregnancy and further development of the embryo deserves to be emphasized.

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