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CASE REPORT

Pathogenetic correlation of severe sepsis and multiple organ dysfunction syndrome provoked by multiple infections in perinatal period of women

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***Short title:** Severe sepsis and MODS in perinatal period*

What is not yet known on the issue addressed in the submitted manuscript

At the moment, there are not exact pathogenetic mechanisms of uncontrolled systemic inflammatory response that is activated by multiple infections in perinatal period especially provoked by *Stenotrophomonas Moltrophilia*. But, if inflammation is not limited and becomes generalized, it can result in the constellation of signs and symptoms of a systemic inflammatory response syndrome (SIRS). The spread of the infection from the primary infected organ through the blood may result in systemic endothelial activation and precipitate sepsis, severe sepsis, and septic shock. Progression of sepsis to shock may lead to multiple organ dysfunction syndrome (MODS) and ultimately death.

The research hypothesis

Presentation of a life-threatening condition: septic shock with MODS resulting from multiple-antibiotic-resistant infections during pregnancy, perinatal period, child-birth.

The novelty added by manuscript to the already published scientific literature

It has been explained the pathogenetic correlation between severe sepsis and MODS provoked by multiple infections from the genital and urinary tracts in women within perinatal period. We report a case of refractive puerperal hematoma that developed progressively during two hours complicated with puerperal sepsis and multiple organ dysfunction syndrome (MODS) followed by an uncomplicated and nontraumatic vaginal delivery.

Abstract

Introduction. Despite significant advances in diagnosis, medical management and antimicrobial therapy, sepsis in the puerperium remains an important cause of maternal morbidity and mortality. The abnormalities associated with the clinical syndrome of sepsis result from a nonspecific innate inflammatory response. This is due to the fact that sepsis represents a systemic inflammatory response syndrome (SIRS) to infection or injury; therefore, it can rapidly progress to septic shock and death despite aggressive treatment. Severe sepsis with MODS has a mortality rate of 20–40%, rising to around 60% if septicemic shock develops. Symptoms of sepsis may be less distinctive than in the non-pregnant population and are not necessarily present in all cases; therefore, a high index of suspicion is necessary. The major pathogens causing sepsis in the puerperium are: group A streptococcus (*GAS),* also known as *Streptococcus pyogenes*, *Escherichia coli, Staphylococcus aureus, Streptococcus pneumonia*, methicillin-resistant *S. aureus* (MRSA), *Clostridium septicum*, *Morganella morganii* and antibiotic-resistant *Stenotrophomonas Moltrophilia*. Multiple risk factors for maternal sepsis have been identified: obesity, impaired glucose tolerance/diabetes, impaired immunity/immunosuppressant medication, anemia, vaginal discharge, history of pelvic infection, amniocentesis and other invasive procedures, cervical cerclage, prolonged spontaneous rupture of membranes, caesarean section, wound hematomas, retained products of conception, GAS infection, vaginal trauma.

Material and methods. Presentation of case report using the following key-words: „infection", „systemic inflammatory response syndrome (SIRS)", „severe sepsis", „septic shock", „multiorgan dysfunction syndrome (MODS)".

Results. We present a case of perinatal infections complicated with MODS.

Conclusions. The presence of pelvic hematomas triggers the sepsis caused by multiple infections in perinatal period and can significantly increase the morbidity related to bleeding, infection, surgery and blood product transfusion. The clinical situation may worsen in the presence of pre-existing pathological conditions before pregnancy.

Key words: perinatal infections, pelvic hematomas, systemic inflammatory response syndrome, septic shock, multiorgan dysfunction syndrome

Introduction

The presence of microorganisms causes inflammation that represents the response of damaged tissues to multiple infectious pathogens. Injured cells release preformed mediators (e.g., histamine) and synthesize proinflammatory substances, including eicosanoids (e.g., prostaglandins, thromboxane, and leukotrienes) and the cytokines (interleukin [IL]-1 and tumor necrosis factor [TNF]–α. These mediators are responsible for the initiation of a nonspecific inflammatory response. Microbial invasion is recognized by the immune system including endotoxins (lipopolysaccharide; LPS) and exotoxins from gram-negative bacteria as well as peptidoglycans (PGs), lipoteichoic acids (LTAs), enterotoxins, and super antigenic exotoxins from gram-positive bacteria [1]. The systemic activity of these proinflammatory mediators may result in an excessive, and often detrimental, response. SIRS is widespread endothelial activation, resulting in the increased production of vasoactive mediators and alteration of vascular homeostasis. Inflammatory cytokines (e.g., IL-1, TNF-α) are responsible for activation of the endothelium, and the activated cells produce inflammatory cytokines as well as increased amounts of NO (via inducible NO synthase), prostaglandins (via inducible cyclooxygenase-2), and endothelin-1 [2].

The initial effect of SIRS is pulmonary vasoconstriction leading to pulmonary hypertension [3] likely caused by thromboxane A_2 [4]. The initial hypertensive phase is followed by systemic hypotension caused by decreased arterial tone and results in decreased left ventricular preload, combined with venous vasodilation in the large-capacity vessels that decreases venous return.

The progression of these processes affecting the cardiovascular system ultimately results in shock. Shock occurs when cardiovascular function is severely impaired, such that hypotension cannot be corrected with intravenous fluid administration and requiring the use of inotropic and/or vasopressor agents [5]. Shock represents severe cardiovascular dysfunction associated with SIRS and is a primary component of MODS.

Materials and methods.

Analysis has been performed in woman in perinatal period, treated in emergency department of Clinical Municipal Hospital „Gheorghe Paladi” in Chisinau, Republic of Moldova, and obstetrics department from June 2021until august 2021. These effects are likely due to (PGI$_2$; prostacyclin) and iNOS knockout that can progress to the syndrome of hyperdynamic shock, with increases in heart rate and cardiac output developing as compensatory mechanisms to maintain tissue perfusion [6]. This compensatory response is impaired by the reduction in left ventricular preload, combined with the decreased cardiac contractility resulting from myocardial depressants (e.g., NO, TNF-α, IL-1), decreased myocardial responsiveness to β-adrenergic stimulation, and decreased compliance due to myocardial edema. Changes occurring in the microvasculature further contribute to the impairment of tissue perfusion. Progres-

sive alteration of the microcirculation leading to failure may represent the common final pathway of SIRS-related injury contributing to or resulting in MODS.

Case report

Patient, 25 years-old, gravida 1, para 0, at 41-42 weeks of gestation, was admitted to the emergency department of Clinical Municipal Hospital „Gheorghe Paladi” in Chisinau, Republic of Moldova because of irregular, painful contractions during the last two weeks. Over eight hours of monitoring she was transferred to the obstetrics department with the onset of labor. From history: the desired pregnancy, visits to the family doctor were not regular. At 24 weeks she had an acute respiratory infection with a fever of 38℃, 4-5 days after the fever the smell and taste disappeared. She was treated unkindly at home. The COVID-19 test did not perform it. On the recommendation of the family doctor during pregnancy administered urinary antiseptics. Aggravated allergic history (cannot specify from which drugs). At a dilation of the cervix of 6 cm, considering the uterine contractions with pronounced pain syndrome and the exhaustion of the parturient in labor as well as at the request of the parturient epidural analgesia was performed. After 10 hours of labor, she delivered a male infant with a weight of 3800 gr., Apgar score 7/8 points. The umbilical cord wrapped once around the neck. The foul-smelling amniotic fluid was with meconium. No obstetrical maneuver was used to assist the delivery. A small median perineal and left vaginal rupture were sutured. Two hours later, she developed signs of shock. The patient complained of marked suprapubic pain, chills, and general weakness. The general condition of medium severity was assessed. The skin was pale, clean, fever 38.2℃, respiratory rate 16/min, pulse 96 b/min, BP 80/60 mmHg, and soft abdomen, sensitive to palpation in the suprapubic region.

The uterus was at the level of the umbilicus, well contracted, lochia in moderate amounts. The urination was free, painless. Given the immediate postpartum period complication with fever 38.2℃, leukocytosis 28.5x10⁹/L, immediately, intravenous access was established and it was indicated Cefazolin 2 g i/v (after performing the sensitivity test), Gentamicin 80 mg i/v, sol. Dexamethasone 8 mg i/v and Ringer solution 500 i/v with monitoring of vital signs. After 15 minutes, the patient's condition worsens: pain become stronger, pulse 130 b/min, BP 80/60 mmHg.

The patient was returned to the operating theater. Examination under general anesthesia revealed a large vaginal hematoma involving the entire right vaginal wall, displacing the uterus upwards and to the left. Uterine massage and manual control of the uterine cavity was performed during which 300 ml of clots were removed. Uterus under manual control was intact, well contracted. The vaginal hematoma (outside the intact vaginal mucosa) was opened and drained and 600 ml of clot blood was removed. The hematoma lodge and vagina was packed with gauze. The estimated overall blood loss was 1500 ml. The patient received transfusion with 2 units of packed red blood cells plus 8 units of fresh

frozen plasma, 3500 ml crystalloids and was given antibiotics. After the operation hemoglobin was 6.5 mmol/L and the clotting factors were stabilized. Lactate level was 2.2 mmol/l. Through the Foley catheter for 2 h 30 min from vaginal tamponade urine was absent. To exclude the possibility of the bleeding dissecting retroperitoneally or trauma of internal organs abdominal sonography was performed. The scan revealed a residual 5x6x2 cm sub peritoneal hematoma in the right side, but no sign of enlarging after compression. The kidney on the right slightly enlarged in size. Injuries to internal organs were not found. The patient was transferred to intensive care unit with oligo-anuria. Furosemide diuresis stimulation was tried without effect and after the decision of the medical council, with the arguments of Acute Renal Injury anuric phase more than 24 hours, severe metabolic acidosis in progression, it was decided to connect the patient to hemodiafiltration and continue broad-spectrum antibiotic therapy. After thirty-two hours delivery the cuff was removed without giving the patient anesthesia. No further bleeding was seen.

Despite intensive care, the patient's condition remained serious. Daily investigations were performed: abdominal USG, pelvic, pleural, echo-cord, monitoring of CBC, urine test, PCR, procalcitonin, lactate level, cultures (blood culture, uroculture, from nasopharynx and vagina) abdominal CT, chest CT. The patient is allergic to blood components, especially albumin. At the 8th day postpartum the ultrasonography of the abdominal cavity reveals: parenchymal organs without pathology, free fluid was absent in the abdominal cavity, pleural fluid on the right – 200-300 ml, on the left – 600-800 ml. The calyx/basin system was not dilated, emphasizing the pyramid design. Pathological fluid in the pericardium was absent. The uterus was normal (127.4 x 59.4 mm), and there was free fluid in the pouch of Douglas of 26.7 mm.

On the 15th postpartum day, the patient's condition was assessed as very serious, caused by Sepsis, acute renal injury, Respiratory Insufficiency gr. I-II on the basis of basal bilateral (septic) pneumonia. At the examination in the council, the following conduct was established: continuation of antibiotic therapy, repeated initiation of hemodiafiltration, correction of anemic syndrome with intravenous iron preparation, erythropoietin, initiation of cytosorb therapy, for contractile purposes to be administered tab. Misoprostol per rectum, gastroprotection, vitamin therapy, dynamic monitoring of PCR, procalcitonin, lactate, biochemical markers of liver function, hepatoprotectives, expectorants, bronchiolitis.

Due to the progression of the free fluid in the peritoneal cavity of more than 1000 ml, procalcitonin level 2.5 ng/mL, lactate level 4.5 mmol/l, on 18th day a diagnostic laparoscopy was performed during which 1500 ml of serocitrin peritoneal fluid were evacuated. Intraoperatively, pelvis-peritonitis was found to have a tendency to spread due to polyserositis as a result of the septic process. Uterus enlarged at 10-11 weeks, pale pink, normal appearance, bilateral ovaries 3x3 cm in diameter, with normal appearance, free fallo-

pian tubes, and free fimbriae. On the right serous tube with hemorrhagic imbibition. On the right flank, in the projection of the round and infundibular-pelvic ligament: hemorrhagic imbibition of the parietal peritoneum because of the tamponade of the postnatal vaginal hematoma. Normal-looking liver, insignificantly enlarged, unstressed gallbladder with an omentum adhesive flange. Intestinal loops, omentum without peculiarities. The free fluid was aspirated from the flanks and the Douglas space. Peritoneal fluid was taken for bacteriological examination. Drained abdominal cavity with 3 tubes. Insignificant blood emission. Postoperative diagnosis: The 19th postpartum day. Pelvis- peritonitis. Sepsis.

Chest x-ray on the 20th postpartum day: Bilateral basal pneumonia with pleurisy. The thoracic surgeon performed the pleural cavity puncture, and then drained the pleural cavity on the right, removing 900 ml of serous fluid. The puncture procedure was complicated by right hemothorax. Belau drainage was applied to the right pleural cavity. On the 21st postpartum day, the patient's condition worsened repeatedly, with gastrointestinal bleeding, which was stopped and conservatively treated with hemostatics. Erosive esophagitis was found on fibro-gastro-duodenoscopy. On ultrasonography: biliary stasis. Insignificant changes in the pancreas. In the iliac fossae, free fluid in small amounts. Postpartum uterus. Clean uterine cavity. Bacteriological examinations collected from drains, urine, and vagina found the presence of *Stenotrophomonas Moltrophilia* with multidrug resistance.

At the 28th postpartum day, considering the serious condition of the patient with the appearance of clinical signs of purulent endometritis, peritonitis, progressive increase in leukocytosis (from 19.9 on 07.07.21 to 26.7 on 08.07.21), procalcitonin level 18 ng/mL, lactate level 7.2 mmol/l, the increased volume of free fluid in the abdomen found by ultrasonography, total hysterectomy without appendages was recommended, which was performed. Intraoperatively, 1.5 liters of ser-citrine content was aspirated when the abdominal cavity was opened. In the small pelvis, the uterus was enlarged at 10-11 weeks, flabby, pale gray, bilateral ovaries measuring 3x3 cm, with a normal appearance, free fallopian tubes, and free fimbriae. On the right flank in the projection of the round ligament towards the right iliac fossa, a conglomerate is palpably determined by the posterior sheet of the parietal peritoneum, medium hardness, immobile, of 5 cm. The Douglas space was free. A total hysterectomy with bilateral tubectomy was performed. The abdominal cavity was washed and drained. Douglas space drained with biluminal tube. At the level of the formation on the right flank, an incision was made on the parietal wall of about 5 cm, an organized hematoma of 5 cm was visualized, it was drained, the capsule was partially removed, the cavity processed with hydrogen peroxide solution, instead of the abscess applied 2 tubes of transcutaneous drain, parietal peritoneum in the incision region sutured with continuous vicril thread. Postoperative diagnosis: 28th puerperal day. Sepsis. Polyorganic insufficiency. Acute kidney damage. Respiratory failure. Heart failure. Liver failure. Puerperal metro endometritis. Organized parametrical hematoma.

On the 32nd postpartum day, positive dynamics were found on repeated radiography. Pneumonia on the right has been absorbed. Transparent left lung. Liquid was obtained from the anterior and posterior drains in minimal quantities, the posterior drain was extracted. On the 33rd day, the anterior pleural drain was extracted.

The patient's medical condition improved rapidly over the next few days. On the 34th day, the patient's condition was assessed as severe-moderate. Hemodynamically stable. Effective spontaneous breathing. Body temperature 36.7°C. Soft, painless abdomen. Laboratory tests were with improvement. She was transferred to the obstetrical department. On the 38th day in a satisfactory condition, she was discharged at home with recommendations. Drug treatment: erythrocyte concentrate 44 doses, fresh frozen plasma 6 doses, Albumin (200 ml) - 5 doses, Vancomycin 300 mg, Imipenem 1000 mg, Colestin 1 mln, Lincomycin 600 mg, Fluconazole 400 mg, Levofloxacin 500 mg, Amicacin 500 mg, Linezolid 1200 mg, Doxacycline 100 mg, Meropenem 500 mg, Ciprofloxacin 400 mg, Metrogil 500 mg , Ceftriaxon 2 gr, Clexan 0.2 ml, / hemostatic Etamzilat 500 mg, Furosemide, Mannitol, Pantoprazole, Heptral, Ademetionine, Hepamethionine, Linex, Panzimed, Venofer 100 mg, Erythropoietin 0.3 ml, Vit. B1, B12, B6, C, Folic acid 5 mg.

Discussion

Vaginal hematomas can develop rapidly and lead to significant pain and maternal hemodynamic compromise. Prompt recognition and management is required to prevent adverse outcomes. They are classified as vulvar, vaginal, vulvovaginal or retroperitoneal. The majority of puerperal hematomas are vulvovaginal and can involve even branches of the uterine artery and of the internal pudendal artery [7]. However, the hemorrhage can also be of venous origin since the veins of the perineum are valveless and have free anastomoses with large intrapelvic venous plexuses [8, 9]. Most hematomas will present within 24 hours of delivery. Perineal pain and pressure are common presenting symptoms along with a palpable tender mass [10].

Management of puerperal hematomas is controversial. Conservative management, surgical intervention and selective arterial embolization are the three main methods for managing puerperal hematomas. Conservative management consists of pressure packing, ice packs, analgesia and close surveillance [11]. Surgical intervention is indicated in cases of acute expansion, large hematomas or unsuccessful conservative management. It includes incision, evacuation of clots and ligation of the bleeding if identified, although in many cases, the lacerated vessel cannot be identified since the bleeding is venous in nature and from multiple sites. A layered closure should be performed to secure hemostasis. A vaginal pack or a balloon tamponade can be left in place for 12 to 24 hours. When mainstay methods of suture and packing fail or when arterial bleeding is identified, transcatheter arterial embolization becomes an interesting alternative [12]. The clinical situation may worsen in the presence of pre-existing pathological conditions before pregnancy.

In our patient the most common reason of severe sepsis is considered infection insult (association of multiple bacteria, viruses and fungi). Specific infections trigger a complex of pathophysiologic response such as inflammation and coagulation. Sepsis results when infections trigger a localized inflammatory process that than spreads with systemic symptoms of fever or hypothermia, tachycardia, tachypnea, leukocytosis or even leukopenia, altered mental state, and hyperglycemia in the absence of diabetes mellitus). These clinical symptoms are called systemic inflammatory response syndrome (SIRS).

SIRS such as syndrome comprises local and systemic manifestations. Local manifestations are characterized by vascular changes and leukocyte infiltration. Vascular reactions are changes in small blood vessels at the site of injury- vagina and perineum (persistent and paralytic arterial hyperemia and venous hyperemia, both of them associated with increased permeability of capillaries vessels walls with a resultant increase in capillary blood flow, causing heat and redness, which are two of cardinal signs of inflammation. This is accompanied by an increase in vascular permeability with outpouring of protein rich fluid (exudate) into the extravascular spaces. Accumulation of exudate in the tissue spaces, producing the swelling and impaired function of vagina and perineum. As fluid moves out of the vessels, stagnation of flow and clotting of blood occur. This aids in localizing the spread of infectious microorganisms.

Under optimal conditions, the inflammatory response remains confined to localized area. In our case (aggravated allergological history, compromised immune system), local inflammation results in prominent systemic manifestations as inflammatory mediators (IL-1, IL-6, TNF-α) are released into the circulation. The most prominent systemic manifestations of inflammation include the acute-phase response, leukocytosis and fever.

The acute phase response, which usually begins within hours or days of the onset of inflammation and/or infection, includes changes in the concentration of plasma proteins (e.g. acute phase proteins), skeletal muscle catabolism (muscles weakness), elevated erythrocytes sedimentation rate, and leukocytosis. These responses are generated by the release of cytokines, particularly IL-1, IL-6, TNF-α. These cytokines affect the thermoregulatory center in the hypothalamus to produce fever, the most obvious sign of the **acute phase response.** IL-1 and other cytokines induce an increase in the number and immaturity of circulating neutrophils by stimulating their production in the bone marrow. Other manifestations of acute phase response include anorexia, somnolence and malaise because of the actions of IL-1 and TNF -α on the central nervous system. The metabolic changes, including skeletal muscle catabolism, provide amino acids that can be used in the immune response and for tissue repair.

In severe bacterial infections (**sepsis),** the large quantities of microorganisms in the blood result in an uncontrolled inflammatory response with the production and release of enormous quantities of inflammatory cytokines

(most notably IL-1 and TNF-α and development of what is referred to as **SIRS.**

These cytokines cause generalized vasodilation, increased vascular permeability, intravascular fluid loss, myocardial depression, and circulatory shock.

Severe sepsis clinically is manifested by arterial hypotension, hypoxemia, oliguria, metabolic acidosis, edemas, thrombocytopenia, myocardial depression, and circulatory shock.

The pathogenesis of sepsis involves a complex process of cellular activation resulting in the release of proinflammatory mediators such as cytokines; recruitment of neutrophils and monocytes; involvement of neuroendocrine reflexes; and activation of compliment, coagulation, and fibrinolytic systems. Initiation of the response begins with activation of the innate immune systems by pattern-recognition receptors (e.g., Toll-like receptors [TLR]) that interact with specific molecules present on microorganism. Binding of TLRs to epitopes on microorganisms stimulates transcription and release of a number of proinflammatory and anti-inflammatory mediators. Two of these mediators, TNF-α and IL-1, are involved in leukocyte adhesion, local `inflammation, neutrophil activation, suppression of erythropoiesis, generation of fever, tachycardia, lactic acidosis, ventilation-perfusion abnormalities, and other signs of sepsis. Although activated neutrophils kill microorganisms, they also injure the endothelium by releasing mediators that increase vascular permeability. In addition, activated endothelial cells release nitric oxide, a potent vasodilator that acts as a key mediator of septic shock.

Another important aspect of sepsis is an alteration of the procoagulation- anticoagulation balance with an increase in procoagulation factors and a decrease in anticoagulation factors. Lipopolysaccharide on the surface of microorganism stimulates endothelial cells lining blood vessels to increase their production of tissue factor, thus activating coagulation. Fibrinogen is then converted to fibrin, leading to the formation of microvascular thrombi that further amplify tissue injury. In addition, sepsis lowers levels of protein C, protein S, antithrombin III, and antithrombin III, and tissue factor pathway inhibitor, substances that modulate and inhibit coagulation. Lipopolysaccharide and TNF-α also decrease the synthesis of thrombomodulin and endothelial protein C receptor, impairing activation of protein C, and they increase the synthesis of plasminogen activator inhibitor-1, impairing fibrinolysis.

Sepsis and septic shock typically manifest with hypotension and warm, flushed skin. Septic shock often presents with a decrease in systemic vascular resistance. There is hypovolemia due to arterial and venous dilation, plus leakage of plasma into interstitial spaces. Abrupt changes in cognition or behavior are due to reduced cerebral blood flow and may be early indications of septic shock. Regardless of the underlining cause, fever and leukocytosis are present. An elevated serum lactate or metabolic acidosis indicates anaerobic metabolism due to tissue hypoxia or cellular dysfunction and altered cellular metabolism. Tissue hypoxia produces continued production and activation of inflammatory mediators, resulting in further increases in vascular permeability, impaired vascular regulation, and altered hemostasis.

Septic shock usually may lead to **MODS (Multiple Organs Dysfunction Syndrome). MODS** represents the presence of altered organ function in an acutely ill patient that such homeostasis cannot be maintained without intervention.

MODS pathogenetically can be explained by the release of proinflammatory mediators (TNF- α, eicosanoids, proteases, platelet-activated factors, and oxidant generating enzymes). The imbalance between pro-and anti-inflammatory mediators with exceed levels of proinflammatory mediators or reduced levels of anti-inflammatory factors such as (soluble TNF receptor, IL-1 receptor antagonist and transforming growth factor).

Secretion of proinflammatory mediators increases the expression of adhesion molecules and increases the margination of blood cells such as platelets, that further reduces blood flow. At level of the liver plasma-derived mediators are synthesized as well as complement factors, acute-phase proteins and factor XII (Hageman factor activation). All of them increase the inflammatory cascade triggering **cardiac and pulmonary** injury accompanied by hepato-enteric syndrome.

Conclusions

The presence of pelvic hematomas in case of sepsis can increase significantly morbidity related to blood loss, infection, and surgery and blood product transfusion. The clinical situation may worsen in the presence of pre-existing pathological conditions before pregnancy.

Declarations of conflict of interests

Nothing to declare.

Authors' contribution

All authors have read and approved the final version of the manuscript

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