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Amniotic fluid embolism – review and multicentric case analysis

Embolie plodovou vodou – přehled a multicentrická případová analýza

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Summary: Amniotic fluid embolism (AFE) is a rare and often fatal obstetric complication, characterized by sudden cardiovascular collapse, dyspnea, seizures, mental alteration or coma and laboratory and clinically diagnosed disseminated intravascular coagulation (DIC). Patient's reaction is typically biphasic with initial pulmonary hypertension and right ventricular failure, followed by left ventricular failure during or immediately right after labor. Early recognition of AFE is critical to a successful survival. Aggressive shock management is needed in collaboration with an anesthesiologist. Several aspects of the condition remain a controversy. This review critically examines, from the best available evidence, the current knowledge regarding the epidemiology, pathophysiology, diagnosis, and available treatment of AFE. This diagnosis still determines perinatal morbidity and mortality and potential permanent neurological symptoms for surviving patients.

Key words: amniotic fluid embolism – disseminated intravascular coagulation – meconium – Zinc-coproporphyrin

Souhrn: Embolie plodovou vodou (AFE – amniotic fluid embolism) je vzácná, velmi závažná a často fatální porodnická komplikace. Je charakterizována náhle vzniklou alterací psychického stavu s kardiovaskulárním kolapsem a probíhající diseminovanou intravaskulární koagulací (DIC – disseminated intravascular coagulation). Reakce organismu na AFE je bifázická. Nejprve reaguje organizmus na cizorodé partikule v plicním řečišti vazokonstrikcí s iniciálně se rozvíjející plicní hypertenzí, která se klinicky manifestuje dušností, tachypnoí a křečemi s následným selháváním pravostranných srdečních oddílů. Ve druhé fázi, která může nebo nemusí volně navazovat na první fázi, dochází v důsledku přetrvávání plicní hypertenze a pravostrannému srdečnímu selhávání k navazujícímu levostrannému srdečnímu selhání a postupnému rozvoji generalizované periferní vazodilatace. Rozvíjející se DIC a selhávající krevní oběh jsou hlavními příčinami rychle postupující alterace celkového stavu postižené pacientky a proto je rychlá a účinná terapie nutností pro zvládnutí situace, pokud u pacientky byť jen diferenciálně diagnosticky na AFE pomýšlíme. Tato diagnóza stále velice ovlivňuje perinatální morbiditu a mortalitu a u přeživších pacientek mohou přetrvávat závažné neurologické obtíže.

Klíčová slova: embolie plodovou vodou – diseminovaná intravaskulární koagulace – mekonium – Zinc-coproporfyrin

Introduction

Amniotic fluid embolism (AFE) is one of the rare but most serious and worst diagnosable conditions in obstetrics. The presence of amniotic fluid in the maternal bloodstream during delivery was first recorded by Professor Meyer in 1926 [1]; clinical presentation and symptoms were first described by Steiner and Lushbaugh in 1941 [2]. Although for decades of efforts trying to explain the whole process of amniotic fluid embolism through the examination of pathophysiological and immunological mechanisms, the exact etiology and pathophysiology of the maternal reaction remain unknown.

An important part of the therapeutic process is the early recognition of risk factors in patients affected by AFE. Unfortunately, no associated risk factors are known; therefore, the clinically significant diagnosis of amniotic embolism remains unpredictable.

The incidence of amniotic fluid embolism varies in the literature from 1 in 15,000 to 1 per 55,000 deliveries, but the exact statistics are not known [3]. Maternal mortality from the disease is very high at around 25%, although thanks to progress in intensive medicine, a large proportion of patients can be saved by early interventions [4]. Only 15% of pa-

tients who survive the shock phase remain without permanent neurological consequences [5].

AFE was first described as a clinical syndrome characterized by the presence of amniotic fluid and parts of fetal tissue in the maternal pulmonary circulation, causing pulmonary tract blockage and the development of pulmonary hypertension. In the original description, Steiner and Lushbaugh recorded the presence of mucin, an amorphous eosinophilic material, and squamous cells in mothers who underwent amniotic fluid embolism. However, parts of fetal tissue were also found in mothers without clinical symptomatology indicative of amniotic fluid embolism [6];therefore, the development of the anaphylactoid maternal reaction based on immunological stimuli from fetal tissue [7] is now accepted rather than the classical pathophysiological mechanism of thromboembolism. Amniotic fluid contains many vasoactive and procoagulant substances, including platelet activating factor, cytokines, bradykinin, thromboxane, leukotrienes and other arachidonic acid derivatives [8] that can seriously affect the maternal bloodstream. This theory of pulmonary vasoconstriction and pulmonary microembolization explains why fetal cell material may be missing from the autopsy reports of mothers who were considered to suffer from amniotic fluid embolism with all typical symptoms. This immunological hypothesis leads us to describe amniotic fluid embolism as an anaphylactoid syndrome associated with pregnancy that explains the decreased concentrations of C3 and C4 complement complexes in mothers who have undergone amniotic fluid embolism [9]. The anaphylactic reaction was first associated with the pathophysiology of amniotic fluid embolism in 1956 by Attwood [10]. Anaphylactoid reaction is called non-IgE degranulation of the mast cells and subsequent excretion of histamine with clinically evident vasodilatory hypotension [11].

Incidence

The approximate incidence of amniotic fluid embolism ranges worldwide between 1: 8,000 – 1: 80,000 [12]. Mortality rates for this diagnosis are very high, but relevant data are not available. The exact and definitive diagnosis is established only ex post by autopsy report. Since peripartum morbidity and mortality are not subject to compulsory reporting, we can only use data from literature.

In 1926, Meyer first described fetal tissue in the pulmonary circulation of a mother who died suddenly of childbirth, but it was not until 1941 that Steiner and Lushbaugh's nosological unit was associated with sudden death during delivery and defined as amniotic fluid embolism. Steiner and Lushbaugh calculated the incidence of this newly described disease as 1 : 8,000, but this calculation was certainly greatly overestimated, because another 26,000 deliveries were performed without this complication. The actual incidence is difficult to assess statistically due to the issue of diagnosis and the absence of reports of subclinical and non-fatal cases. We are in a similar situation with the question of maternal and perinatal mortality. The data are not consistent in the Czech Republic or worldwide, and therefore mortality is only estimated and corrected according to individual case reports – for Great Britain, the latest population study reports maternal mortality at around 24% and in the US around 21%; perinatal mortality associated with amniotic fluid embolism has ranged between 10–44% [13] in recent decades, according to these studies.

Risk factors

Until recently, risk factors were obtained from individual case reports, autopsy reports and occasional reviews. In 2009, two comprehensive population retrospective cohort studies compiled and reviewed data of 3 million hospitalized mothers looking for significant links between AFE and potential risk factors [14,15]. Factors significantly increasing the risk of AFE include maternal age over 35 years, cesarean section or other form of operative delivery (forceps delivery, vacuum extraction), placental disorders (placenta previa, placental abruption), preeclampsia and fetal distress. Reverse causality is possible in operative deliveries and fetal distress. In the Canadian study, they followed up the riskiness in polyhydramnios, cervical laceration and uterine rupture. The question remains in induced labor in the Canadian study with increased risk of AFE almost twice as high as spontaneous childbirth. The American study did not confirm this association. The results of these studies may be influenced by the overestimation of "lighter" forms of AFE; retrospective data was based only on medical records. Data from a prospective British AFE study using the UK Obstetric Surveillance System (UKOSS) are still not available.

Pathophysiology

Pathological changes in acute amniotic fluid embolism are predominantly nonspecific and include pulmonary edema, atelectasis, congestion in the pulmonary tract, emphysema and signs of microthrombosis. Larger emboli are not noticeable in the main vessels. Traditional confirmation of pathological diagnosis is based on the presence of fetal tissue from amniotic fluid in the capillaries of the pulmonary tract. Amniotic fluid contains squamous epithelium from the skin of the fetus, fetal meconium mucin, fat amounts of vernix caseosa and fetal hair [16]. These derivatives can be confirmed by dyeing in a light microscope using hematoxylin-eosin stain (individual cells), alcian blue stain (acid mucopolysaccharides), mucicarmine stain (mucus), oil red O stain (fat), or it is possible to use immunohistochemical markers such as cytokeratin AE1/AE3 (according to pathologists of the so-called "pancytokeratin") [17]. Japanese scientists report the use of

monoclonal antibody TKH-2 as the most sensitive method to detect amounts of meconium and AFE-derivative mucin from fetal mucus in lung autopsy specimens compared to conventional staining with hematoxylin-eosin or alcian blue stains [18]. TKH-2 is a sensitive antibody to mucin glycoprotein-sialyl Tn (STN). Fetal tissue was found not only in the lungs of the deceased mother, but also in the capillaries of other organs (e. g., cervix, lower uterine segment, kidneys, heart, liver, spleen, adrenal glands, pancreas and brain [19]).

The pathogenesis of the disease is not entirely clear. The transition of amniotic fluid into maternal circulation is done in the placental barrier by breaking the space between the maternal and fetal compartments allowing particles from amniotic fluid to come through. At the level of endocervical veins, disruption of the uterine mucosa and placental villi occurs as the pressure gradient increases, and the amniotic fluid enters the maternal circulation in increasing amounts. This hypothesis is confirmed by the work in which hypertonic solution with iodine-labeled albumin (^{125}I-labeled albumin) was applied intraamniotic and subsequently detected in the maternal circulation [20]. This mechanism confirms the increased risk of AFE in mothers with placental disorders, operative deliveries, cervical or uterine lacerations and in fetuses with polyhydramnios. Parts of the fetus (fetal debris) trapped in the cervical veins can also enter the maternal bloodstream during involution [21].

The traditional notion of occlusion of the pulmonary veins by amniotic fluid is currently being replaced by an immunological hypothesis, supported by the absence of distinct particles obliterating the pulmonary tract and great interindividual variability in clinical manifestations of AFE. In 1984, Hammersmichdt described the activation of complement in experimental incubation of amniotic fluid and normal plasma. With this experiment, he postulated the possibility of pulmonary failure as the overall response of the organism to a complement-induced granulocytic response [22]. Ten years later, Benson proposed a mechanism similar to the anaphylactic reaction of a healthy organism to exposure to fetal antigens from amniotic fluid. Laboratory levels of women with AFE indicated very low serum concentrations of C3 and C4 complement complexes, which support the notion of complement activation and AFE development [23]. C3 and C4 complement complexes are the main representatives of the organism's humoral defenses; the main function of which is opsonization, chemotaxis and chemical lysis of the cell. Their consumption indicates an inappropriate reaction of the organism to a nonspecific insult in the form of fetal tissue in AFE [24]. In the Czech literature, we can find the equivalent of AFE called the anaphylactoid reaction of the organism during amniotic fluid embolism.

Multifactorial involvement in AFE also affects the blood count and coagulation cascade. In vitro amniotic fluid improves thrombogenic capability by creating a so-called "thromboplastin-like" effect, which accelerates platelet aggregation and activates complement. Amniotic fluid contains tissue factor, which activates factor X by binding to factor VII and initiates the coagulation cascade by the extrinsic pathway and accelerates the development of consumption coagulopathy. The contradiction of these two disrupts the balance of clotting and creates microvascular thrombi on the one hand, causing vasoconstriction in the capillary circulation and, on the other hand, prolonging the time required to form a functional thrombus in the physiological response to postpartum bleeding and unstoppably aggravate massive fibrinolysis by consuming other factors [25]. Using a thromboelastography analysis, we can demonstrate a hypercoagulation condition associated with amniotic fluid exposure to maternal blood and enhanced platelet activation, but there is no evidence for fibrinolytic features of amniotic fluid components. Therefore, consumption of coagulopathic proteins is most likely to be the primary cause of bleeding [26].

Diagnostics

The diagnosis of amniotic fluid embolism is based on clinical symptomatology and is one of the diagnoses per exclusion after excluding all possible explanations of the shock during and after delivery. In an effort to objectify symptoms and contexts, various dependent criteria are available. The most common symptoms are shortness of breath, hypotension, convulsions, maternal disseminated intravascular coagulation (DIC) and fetal hypoxia. Unfortunately, the causality of the last symptom is uncertain. Early diagnosis significantly improves the survival of the mother. The detection of a maternal critical condition during delivery is crucial for subsequent therapeutic steps. Efforts to systematize and implement diagnostic criteria would significantly reduce ambiguities and delays in making urgent decisions. A French study proposed the diagnosis of amniotic fluid embolism using four criteria [27]:

1. Sudden cardiopulmonary arrest or hypotension with respiratory distress (shortness of breath, cyanosis, peripheral oxygenation < 90%).
2. DIC – coagulopathy confirmed without severe blood loss or shock.
3. Onset of clinical signs during childbirth or within 30 minutes after delivery of placenta.
4. Absence of feverish state (body temperature < 38 °C).

About 66% of mothers who died of amniotic fluid embolism met all four of the above criteria [27].

Laboratory tests are still nonspecific (blood count, coagulation tests, Astrup tests, cardiac enzymes, iontogram). Obvious DIC is manifested by prolongation of the international normalized ratio and

partial thromboplastin time (aPTT) with decrease in fibrinogen levels. Cardiac enzymes may be elevated and blood gases confirm hypoxemia. Pulse oximetry indicates total oxygen hyposaturation. X-ray signs are bilateral heterogeneous and homogeneous opacities with unclear pulmonary edema difficult to distinguish from other causes (left-sided heart failure, pneumonia, transfusion-related acute lung injury) [28]. Transesophageal echocardiography may demonstrate right-sided heart failure and dilation of the right-sided heart compartments, but we rarely have a cardiologist available in obstetrics.

Recently, there has been an effort to use special diagnostic markers for AFE and their use in clinical practice. These new methods include detection of Zinc-coproporphyrin, sialyl Tn (STN), tryptase, and complement. Zinc-coproporphyrin is a dye characteristic of meconium amounts, with similarly elevated levels of sialyl Tn, fetal meconium antigen and mucin [18]. Likewise, we can use the SCC (squamous cell carcinoma) antigen, which is up to several times higher in the serum in patients with AFE [29]. Tryptase is a marker of mast cell degranulation, and in some studies, elevated serum beta-tryptase enzyme levels are associated with severe AFE [30,31], while some authors describe normal levels [32]. The most promising seems to be a decrease in the levels of C3 and C4 complement complexes, where tests confirm 88–100% sensitivity and 100% specificity with the diagnosis of AFE [23]. The decrease in C3 and C4 levels of the complement complexes is explained by the consumption during activation of the complement cascade in the classical pathway by establishing STN (fetal meconium and mucin component) [24]. Another marker studied is C1INH (C1 esterase inhibitor). The activity of this enzyme was statistically significantly reduced in AFE [33]. C1INH is the main inhibitor of the C1 complement complex, activated factor XII (FXIIa) and kallikrein, thus C1INH affects not only pro-inflammatory factors, but also coagulation [34]. Other markers whose levels deviate from the norm in AFE include IGFBP-1 (insulin-like growth factor binding protein 1), BNP (brain natriuretic peptide), chromogranin A, tumor markers CA 125, CEA, SCC and PSA. Unfortunately, these tests cannot yet be used by bedside methods, and in most hospitals, the results are delayed several days. Diagnostic markers from serum are a promising way for STATIM examinations in case of suspected AFE. In the future, these markers and their evaluation need to be addressed and their use verified in clinical trials.

Treatment

AFE therapy is symptomatic and focuses on ensuring cardiopulmonary stability and adequate oxygenation of maternal tissues as early as possible. If the condition has developed before or during childbirth, we indicate acute caesarean section. The life of the mother has priority over the life of the fetus. Mothers after initial stabilization often need to be hospitalized in the intensive care unit.

Even if AFE is suspected, it is necessary to immediately administer oxygen with a mask, continuously observe vital functions (BP, ECG, SpO2, consciousness), call an experienced obstetrician and anesthesiologist and a sufficient number of paramedical staff. It is necessary to keep documentation in accurate chronological order.

As part of AFE therapy, we pursue the following basic objectives [35]:

1. Ensuring sufficient oxygenation – we administer oxygen with a mask. When needed, the anesthesiologist initiates mechanical ventilation with OTI. It is often necessary to include a high PEEP (positive end-expiratory pressure).
2. Maintaining cardiac output and blood pressure – volumotherapy is essential. If possible, a central venous catheter (CVC) is inserted to provide adequate intravenous therapy. To optimize volumotherapy, it is advisable to use ECHO, as well as monitoring using the established CVC and arterial catheter. Administration of crystalloids and colloids is indicated; vasopressors are administered in refractory hypotension (adrenaline is the drug of choice as in other anaphylactoid reactions, noradrenaline and dobutamine can be administered continuously). Due to the fact that even with adequate oxygen therapy in maternal anemia, fetal hypoxia may occur, so we do not hesitate to administer transfusions to the mother.
3. Coagulopathy therapy – we follow general recommendations for life-threatening bleeding.
4. Stabilization of the internal environment and its disorders.

We also check for DIC manifestations such as uterine bleeding, puncture bleeding, and petechiae. Administration of hydrocortisone at a dose of up to 2 g per 24 hours reduces pulmonary vasospasm and pulmonary edema. In addition, the cardiac response to catecholamines may be potentiated.

AFE treatment includes supportive and non-causal therapy requiring intensive management. Monitoring includes pulse oximetry, strict monitoring of intake and output, monitoring of blood pressure, regular sampling and monitoring of changes in coagulation, capnometry, inserting of an arterial catheter for more accurate monitoring of cardiac output, and central venous pressure. Transesophageal echo is preferably used to refine the response to infusion therapy in order to avoid a high preload exposure. In the first moments, correction of hemodynamic instability is important, as well as the therapy of coagulation disorders by administration of fresh plasma and platelet concentrate. The administration of cryoprecipitate in DIC therapy containing fibronectin, which facilitates the removal of fetal components using the monocyte-macrophage system [36],

also seems to be ideal. Meanwhile, the only alternative is the administration of antifibrinolytics aprotinin and serine proteinase inhibitor FOY in clinical studies, but without major clinical use yet [37,38]. The main goal is to evaluate and analyze statistical local data which are often inconsistent due to troublesome definitions [39].

Case report 1

A case of a 33-year old healthy primipara in the 39th week of pregnancy. She was diagnosed with gestational diabetes and put on a diabetic diet, but otherwise with an insignificant medical history. The patient was sent for admission from a prenatal outpatient's department for a newly diagnosed gestational hypertension suspected of an incipient preeclampsia according to a blood pressure decompensation and PEI 267. During hospital admission, blood pressure gradually normalized without any medication, the patient was without any preeclamptic symptoms, the cervix was closed and the fetus ultrasound was normal (eutrophic fetus, doppler flowmetry in normal range). Because of the incipient preeclampsia suspicion, we initiated induction of labor by inserting an intracervical Foley catheter. Next day, we continued inducing labor with 25 µg Mispregnol tablets per os every two hours until the sixth tablet per day. After every Mispregnol application, cardiotocography (CTG) was performed. The day after at 5 am, amniotic membranes spontaneously ruptured and at 7:59 am, when regular contractions started and the cervix was dilated to 4 cm, the patient was transferred from the ward to the delivery room. During the first stage of labor, the patient's medication was Butylscopolammonium bromide Kalceks 20 mg i.v. in 100 mL FR1/1, and because of secondary weak uterine contractions, 2 IU oxytocin + 500 mL 5% glucose i.v. and 0.5 amp. nalbuphine + 100 mL SS i.v. was used as analgesia. The cervix was fully dilated at 16:11. During the second stage of labor, 2 IU Oxytocin in 100 mL SS (of normal saline) i.v. infusion was administered. Afterwards, the baby was born at 17:02 without any complications. At 17:38, the patient complained about weakness and nausea, but she negated dyspnea or pain. When the doctor came to the delivery box, the patient was oriented and able to communicate with medical staff members but the patient's somnolence was developing very quickly. At that moment, the blood pressure was 61/43 mmHg and heartbeat was 128/min. An oxygen mask was put on the patient's face. The patient delivered the entire placenta with approximately 250 mL of clot. Meanwhile, blood samples were taken – blood count and coagulation. Infusion therapy was started by intravenous bolus injection of 5 IU of Oxytocin and continuous infusion of 10 IU of Oxytocin in 500 mL of 5% Glucose. Two 400 µg tablets of Mispregnol per rectum were inserted. According to the patient's clinical condition and repeated hypotension, the senior consultant and anesthesiologist were called immediately. In the meantime, the birth canal was controlled and assessed as first grade perineal rupture and laceration of the right labium major as the birth injury. Total blood loss was estimated to be about 600 mL. Abdominal ultrasound was performed noting an empty retracted uterus, insignificant (about 150 mL) free fluid behind the uterus, subhepatic area without any free fluid and homogenic hepatal tissue without any signs of hematoma. Cavum Douglasi via rectal ultrasound was also present without a significant amount of free fluid. At that time, there was no indication to perform exploratory laparotomy. As a differential diagnosis, we considered postpartum hemorrhage, amniotic fluid embolism or spontaneous hemoperitoneum in postpartum potential rupture of intra-abdominal organs. Following medication and steps according to the anesthesiologist's record: a second venous access and an arterial access and a central – venous cannula were secured by the anesthesiologist to take another blood sample and to be able to give sufficient circulatory support.

According to the anesthesiologist's record. 2 × 20 mg of ephedrine, 1 g Exacyl, 8 g of Haemocomplettan in total, 10 mL calcium gluconicum and two units of red blood cell transfusions were initially applied. The patient was intubated to be able to compensate for the circulation and for the gynecologist to be able to suture the birth injuries. The first blood results were: Astrup pH 7.2; lactate 2.6–2.9 mmol/L; hemoglobin 142/116/102 g/L and normal results of coagulation tests (during appropriate substitution) and fibrinogen 4.24 (after 8 g of Haemocomplettan). After suturing the birth injuries, blood pressure was still fluctuating even during medical circulatory support by catecholamines (noradrenaline 0.2–1.3 mg/hour). Then, the intubated patient was transferred to the intensive care unit on circulatory support with a nasogastric tube and urinary catheter with diuretic support. At the intensive care unit, thoracic ultrasound was performed by an anesthesiologist without significant enlargement of the right heart chamber or pericardial effusion and the ECG was without any signs of acute cardiac ischemia. At 22:30, the blood results were as follows: Astrup pH 7.233; lactate 1.4 mmol/l; minor hyponatremia and hypomagnesemia; Hs-troponin elevation to 138; proBNP elevation to 114; and leukocytosis at 38.9. The rest of the blood count and coagulation were in the normal range. Based on actual blood results, we initiated antibiotic therapy with Azepo 2 g in 0.9% NaCl 100 mL i.v. every 8 hours and anticoagulant therapy with Fraxiparine 0.3 mL s.c. in 24 hours. At the ICU, blood pressure gradually stabilized and in the morning, we could progressively control the circulatory system with catecholamines. The patient was cardiopulmonary stable and extubated without complica-

tions. On January 11th, chest X-rays and ECHO were performed without any adverse pathological findings. The patient was dismissed on the 10th day after delivery without any clinical problems.

Case report 2

A 28-year-old primigravida with IDGDM (insulin-dependent gestational diabetes mellitus) and diabetic fetopathy (double fetal contours, largest vertical pocket of amniotic fluid at 95 mm) was acutely admitted for renal colic at 36 weeks and 3 days of gestation. Bilateral hydronephrosis was confirmed on ultrasound without signs of infection. Patient was treated conservatively. Initial laboratory investigation only had uric acid elevation of 575 µmol/L, but otherwise completely without pathology. At 37 weeks and 1 day, labor was induced on account of bilateral symptomatic urostasis and diabetic fetopathy. After the application of PGE E2 at 0.75 mg intracervically, regular uterine activity started along with these findings: cervix was in the medium position, had medium consistency, was 1 cm long, and 3 cm dilated. Artificial rupture of the membrane was performed leading to the gush of a large amount of clear amniotic fluid. For beta-haemolytic G streptococcal infection positivity, PNC G 5 MIU was administered i.v. After the amniotomy, the patient suddenly went into shock with a fetal heart rate of 70 bpm and oxygen saturation of 80%. Patient was quickly transferred to the delivery room and started on oxygen by face mask. She complained of chest pain, was cyanotic, tachypneic, and had a blood pressure of 128/98 mmHg, heartbeat of 122/min, and glycemia at 6.2 mmol/L. Oxygen saturation remained at 80% while on oxygen supplementation. Alteration of fetal heart rate persisted. On account of nonreassuring CTG and uterine activity, acute tocolysis at a dose of 10 µg Gynipral i.v. bolus was given. There was a slight improvement in fetal heart rate – 110 bpm, but dyspnea did not improve. Cervical dilation was 4 cm with clear amniotic fluid. Acute cesarean section was indicated for suspected thromboembolism and impending fetal hypoxia. Cesarean section was performed under general anesthesia. The first attempt at invasive blood pressure monitoring was unsuccessful; O_2 saturation at the beginning of the procedure was 70%, and after intubation it rose to 90%. At 12:24, a baby girl was born weighing 3,610 g, with Apgar score of 5/8/9 and pH of 6.78. Uterine hypotonia developed and was initially treated conservatively with uterotonics i.v. and Prostin M15 i.m. The uterus was further contracted. DIC developed: the patient bled from injection sites, cardiopulmonary system was unstable, and hematuria developed. Based on these clinical features, treatment for amniotic fluid embolism was formed. Volume expansion, substitution of blood derivatives and coagulation factors (2 units of plasma, 2 red blood cell transfusions, 2 g Fibrinogen, 2 g Exacyl) were started during the operation. Total blood loss during the surgery was estimated at 2,000 mL, and drains were introduced intraperitoneally, subfascially and subdermally. Diuresis was preserved (300 mL sanguinolent urine). After the operation, the patient was transferred to the ARO RES bed, where massive substitution of a blood derivative and therapy for hypovolemic shock continued. According to the viscoelastogram of ROTEM, afibrinogenemia and hypocoagulation were present. During the stay in the ARO bed, further blood loss to the drains occured within 3 hours of the operation, bleeding from the puncture sites persisted, hematuria, and massive vaginal bleeding also occurred. Fibrinogen 4 + 4 g, 3 units of platelet concentrate, and massive blood transfusions were done. Uterotonics I.V. bolus was administered, and the uterus contracted. During palpation of the uterine fundus, once again 300 mL of blood was lost. Novoseven 10 mg i.v. was administered, and bleeding from the uterus continued, even after NovoSeven. Circulation was dependent on volume expansion, otherwise there was a decrease in blood pressure and tachycardia; it was necessary to support circulation with noradrenaline 0.4 µg/kg/min, blood pressure was 100/60 mmHg, and heart rate was 130/min. Due to the patient's worsening condition, simple hysterectomy was indicated and carried out with noradrenaline support of the circulatory system. Local hemostatic agents were used for diffuse surface bleeding during the procedure – TachoSil patch to the parametrium, on the vaginal stump and under the vesicular term file, and then Surgicel on the abdominal muscles. Total blood loss during the procedure was 600 mL. During the procedure, 3× platelet concentrates, 5× red blood cell transfusions, 5× frozen plasma and 6 g fibrinogen were administered. Hematology reports showed severe hemolysis and non-clotting blood. Due to the shock and DIC, the patient was again transported to the ARO RES bed after surgery, where blood transfusion, DIC therapy and circulatory support continued. Hypofibrinogenemia and coagulation impairment persisted (Quick = 37%, APTT = 83.0, thrombin time = 34.6, fibrinogen = 1.0). Repeated administration of 10 mg Novoseven was given. According to echocardiography, the patient developed right heart congestion – enlargement of the right ventricle and signs of pulmonary hypertension, and according to CT, there was fluidothorax, which drained. There was also elevation of cardiac markers. After 48 hours, there was gradual stabilization of the patient. She was gradually weaned off sedation, and coagulation parameters improved. A total of 24 g of fibrinogen, 20 mg of Novoseven, 8× platelet concentrate, 27× frozen plasma, 31× red blood cell transfusions, and 4,200 units of Prothromplex were administered to the patient. On the 6th postoperative day, the patient was transferred back to the gynecological department in a compensated condition, where we continued complex therapy and parenteral nutrition. According

to the ultrasound and CT, there was a hematoma measuring 43 × 116 × 70 mm in the area of the small pelvis and the vaginal stump, which was static during hospitalization without signs of enlargement. Due to the general condition of the patient, a conservative approach was preferred. Administered long-term antibiotic therapy and targeted antibiotic therapy according to the finding of *E. coli*, α-hemolytic streptococci in the urine. According to follow-up ultrasound examinations, the hematoma in the small pelvis gradually resolved. There were transient signs of hypoperfusion hepatopathy in the laboratory investigations. On the 13th postoperative day, a febrile condition developed with pain in the epigastrium and right hypochondria. According to the clinic, septic conditions vs. developed based on an infected small pelvic hematoma, which were further treated with conservative combination ATB therapy; the condition was further complicated by a toxic allergic rash from Ampicillin. After discontinuation of Ampicillin and i.v. corticotherapy, the rash subsided, and the patient's condition was further stabilized without complications; in the laboratory, there was a noticeable adjustment of coagulation, liver enzymes, and a decrease in proinflammatory markers. The finding was a hematoma in the small pelvis long-term without progression. The patient was discharged on the 21st postoperative day in a stable condition without neurological deficits.

Conclusion

Our observed cases showed variable symptoms for diagnosis of AFE. Fortunately, both women survived and presented no persistent neurological deficits unlike other previously described cases in the Czech Republic [40]. The definitive diagnosis of AFE can only be established with a conclusion from the autopsy reports and after excluding other possible clinical diagnoses. AFE is still a feared complication in obstetrics, and therefore data need to be systematized and stored in global (at least national) registries in the future to address unanswered questions about incidence, mortality and prognosis in patients for whom this diagnosis will be established. Further research on serum markers pointing to AFE may help clinicians with uncertainty in cases where AFE is considered and to allow adequate therapy for the diagnosis. Methods for the detection of Zinc-coproporphyrin, sialyl Tn-antigen, C3 and C4 complement complexes seem to be the most promising. In unexplained hypotension, extensive bleeding and progressive shock without detectable cause, amniotic fluid embolism should always be considered. Immediate complex multidisciplinary support is recommended. Final diagnosis is confirmed only by an autopsy when treatment is not sufficient.

References

1. Meyer JR. Embolia pulmonary amino caseosa. Brasil Medico 1926; 40(2): 301–303.
2. Steiner PE, Lushbaugh C. Maternal pulmonary embolism by amniotic fluid as a cause of obstetric shock and unexplained death in obstetrics. JAMA 1941; 117: 1245–1254.
3. Fitzpatrick KE, Tuffnell D, Kurinczuk JJ et al. Incidence, risk factors, management and outcomes of amniotic-fluid embolism: a population-based cohort and nested case-control study. BJOG 2016; 123(1): 100–109. doi: 10.1111/1471-0528.13300.
4. Conde-Agudelo A, Romero R. Amniotic fluid embolism: an evidence-based review. Am J Obstet Gynecol 2009; 201(5): 445.e1–445.e13. doi: 10.1016/j.ajog.2009.04.052.
5. Gist RS, Stafford IP, Leibowitz AB et al. Amniotic fluid embolism. Anesth Analg 2009; 108(5): 1599–1602. doi: 10.1213/ane.0b013e31819e43a4.
6. Lee W, Ginsburg KA, Cotton DB et al. Squamous and trophoblastic cells in the maternal pulmonary circulation identified by invasive hemodynamic monitoring during the peripartum period. Am J Obstet Gynecol 1986; 155(5): 999–1001. doi: 10.1016/0002-9378(86)90334-0.
7. Clark SL, Hankins GD, Dudley DA et al. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol 1995; 172(4 Pt 1): 1158–1167. doi: 10.1016/0002-9378(95)91474-9.
8. Walsh SW, Wang Y. Secretion of lipid peroxides by the human placenta. Am J Obstet Gynecol 1993; 169(6): 1462–1466. doi: 10.1016/0002-9378(93)90419-j.
9. Benson MD. A hypothesis regarding complement activation and amniotic fluid embolism. Med Hypotheses 2007; 68(5): 1019–1025. doi: 10.1016/j.mehy.2006.09.052.
10. Attwood MD. Fatal pulmonary embolism by amniotic fluid. J Clin Pathol 1967; 9(1): 38–46. doi: 10.1136/jcp.9.1.38.
11. Bochner BS, Lichtenstein LM. Anaphylaxis. N Engl J Med 1991; 324(25): 1785–1790. doi: 10.1056/NEJM199106203242506.
12. Gilbert WM, Danielsen B. Amniotic fluid embolism: decreased mortality in a population-based study. Obstet Gynecol 1999; 93(6): 973–977. doi: 10.1016/s0029-7844(99)00004-6.
13. Lewis G. The confidential enquiry into maternal and child health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer 2002–2005. The seventh report on confidential enquiries into maternal deaths in the UK. London: CEMACH 2007.
14. Kramer MS, Rouleau J, Baskett TF et al. Maternal Health Study Group of the Canadian Perinatal Surveillance System. Amniotic-fluid embolism and medical induction of labour: a retrospective, population-based cohort study. Lancet 2006; 368(9545): 1444–1448. doi: 10.1016/S0140-6736(06)69607-4.
15. Abenhaim HA, Azoulay L, Kramer MS et al. Incidence and risk factors of amniotic fluid embolism: a population-based study on 3 million births in the United States. Am J Obstet Gynecol 2008; 199(1): 49.e1–49.e8. doi: 10.1016/j.ajog.2007.11.061.
16. Attwood HD. Amniotic fluid embolism. Pathol Annu 1972; 7: 145–172.
17. Attwood HD. The histological diagnosis of amniotic-fluid embolism. J Pathol Bacteriol 1958; 76(1): 211–215. doi: 10.1002/path.1700760124.
18. Kobayashi H, Oi H, Hayakawa H et al. Histological diagnosis of AFE by monoclonal antibody TKH-2 that recognizes NeuAc alpha 2-6GalNAc epitope. Hum Pathol 1997; 28(4): 428–433. doi: 10.1016/s0046-8177(97)90031-9.
19. Balazic J, Rott T, Jancigaj T et al. Amniotic fluid embolism with involvement of the brain, lungs, adrenal gland, and heart. Int J Legal Med 2003; 117(3): 165–169. doi: 10.1007/s00414-003-0368-5.
20. Talbert LM, Adcock DF, Weiss AE et al. Studies on the pathogenesis of clotting defects during salt-induced abortions. Am J Obstet Gynecol 1973; 115(5): 656–662. doi: 10.1016/0002-9378(73)90614-5.
21. Courtney LD. Amniotic fluid embolism. Br Med J 1970; 1(5695): 545. doi: 10.1136/bmj.1.5695.545.
22. Hammerschmidt DE, Ogburn PL, Williams JE. Amniotic fluid activates complement. A role in amniotic fluid embolism syndrome. J Lab Clin Med 1984; 104(6): 901–907.
23. Clark SL. New concepts of amniotic fluid embolism: a review. Obstet Gynecol Surv 1990; 45(6): 360–368. doi: 10.1097/00006254-199006000-00003.

24. Busardò FP, Frati P, Zaami S et al. Amniotic fluid embolism pathophysiology suggests the new diagnostic armamentarium: β-tryptase and complement fractions C3-C4 are the indispensable working tools. Int J Mol Sci 2015; 16(3): 6557–6570. doi: 10.3390/ijms16036557.
25. Lockwood CJ, Bach R, Guha A et al. Amniotic fluid contains tissue factor, a potent initiator of coagulation. Am J Obstet Gynecol 1991; 165(5 Pt 1): 1335–1341. doi: 10.1016/0002-9378(91)90363-v.
26. Harnett MJ, Hepner DL, Datta S et al. Effect of amniotic fluid on coagulation and platelet function in pregnancy: an evaluation using thromboelastography. Anesthesia 2005; 60(11): 1068–1072. doi: 10.1111/j.1365-2044.2005.04373.x.
27. Bonnet MP, Zlotnik D, Saucedo M et al. Maternal death due to amniotic fluid embolism: a national study in France. Anesth Analg 2018; 126(1): 175–182. doi: 10.1213/ANE.0000000000002511.
28. Manchanda R, Sriemevan A. Anaphylactoid syndrome caused by amniotic fluid embolism following manual removal of placenta. J Obstet Gynaecol 2005; 25(2): 201–202. doi: 10.1080/01443610500052013.
29. Koike N, Oi H, Naruse K et al. Squamous cell carcinoma antigen as a novel candidate marker for amniotic fluid embolism. J Obstet Gynaecol Res 2017; 43(12): 1815–1820. doi: 10.1111/jog.13453.
30. Fineschi V, Riezzo I, Cantatore S et al. Complement C3a expression and tryptase degranulation as promising histopathological tests for diagnosing fatal amniotic fluid embolism. Virchows Arch 2009; 454(3): 283–290. doi: 10.1007/s00428-009-0730-1.
31. Farrar SC, Ghermann RB. Serum tryptase analysis in a woman with amniotic fluid embolism. A case report. J Reprod Med 2001; 46(10): 926–928.
32. Dorne R, Pommier C, Emery JC et al. Amniotic fluid embolism: successful evolution course after uterine arteries embolization (in French). Ann Fr Anesth Reanim 2002; 21(5): 431–435. doi: 10.1016/s0750-7658(02)00638-x.
33. Tamura N, Kimura S, Farhana M et al. C1 esterase inhibitor activity in amniotic fluid embolism. Crit Care Med 2014; 42(6): 1392–1396. doi: 10.1097/CCM.0000000000000217.
34. Cugno M, Cicardi M, Bottasso B et al. Activation of the coagulation cascade in C1-inhibitor deficiencies. Blood 1997; 89(9): 3213–3218.
35. Černý A, Pařízek A, Šimják P. Embolie plodovou vodou – přehledový článek. Ceska Gynekol 2014; 79(4): 255–259.
36. Rodgers GP, Heymach GJ 3rd. Cryoprecipitate therapy in amniotic fluid embolization. Am J Med 1984; 76(5): 916–920. doi: 10.1016/0002-9343(8491009-x.
37. Stroup J, Haraway D, Beal JM. Aprotinin in the management of coagulopathy associated with amniotic fluid embolism. Pharmacotherapy 2006; 26(5): 689–693. doi: 10.1592/phco.26.5.689.
38. Taenaka N, Shimada Y, Kawai M et al. Survival from DIC following amniotic fluid embolism. Successful treatment with a serine proteinase inhibitor; FOY. Anaesthesia 1981; 36(4): 389 393. doi: 10.1111/j.1365-2044.1981.tb10244x.
39. Korbel M, Krištůfková A, Dugátová M et al. Analýza materskej morbidity a mortality v Slovenskej republike v rokoch 2007–2012. Ceska Gynekol 2017; 82(1): 6–15.
40. Žáková D, Trudáková L, Farhat FS et al. Dvě kazuistiky porodů s příznaky embolismu plodovou vodou v letech 2002–2012 s různými výsledky v Krajské zdravotní a. s., Nemocnice Děčín, o.z. Ceska Gynekol 2015; 80(4): 302–308.

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