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MODERN THERAPEUTIC APPROACH TO AMNIOTIC FLUID EMBOLISM

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ABSTRACT
Amniotic fluid embolism is a devastating obstetric complication that usually occurs during vaginal delivery or cesarean section. To date there is no special treatment. The treatment is supportive and focuses on the rapid stabilization of the cardiorespiratory system, the adequate oxygenation of vital organs and the correction of coagulation. The key to treating the syndrome is immediate recognition, a high rate of clinical suspicion, immediate recovery and delivery of the fetus. In this article, based on the bibliography, we list the basic principles for dealing with this rare obstetric complication.

KEYWORDS: Amniotic fluid embolism, cardiopulmonary resuscitation, bleeding, disseminated intravascular coagulation, treatment.

INTRODUCTION
Amniotic fluid embolism is a catastrophic obstetric complication first described by Ricardo Meyer in 1926.[1] It is a multifactorial syndrome that affects all organs and is characterized by sudden cardiovascular shock, change in mental level and disseminated intravascular coagulation.[2] Absence of classic symptoms and signs of cardiovascular and respiratory failure is extremely rare.[3] It can occur during pregnancy, usually during a normal birth or caesarean section, but also after childbirth in the first days of labor in about a third of cases.[4] Amniotic fluid embolism is uncommon. Based on recent bibliography, it is estimated that it ranges from 0.8 to 1.8 cases per 100,000 pregnancies, with the percentage of women who died or had permanent neurological damage ranging from 30% to 41%.[5]

The pathogenetic mechanism of amniotic fluid embolism to date has not been elucidated with absolute accuracy.[6] A necessary condition for the onset of the syndrome is considered to be the disturbance of the anatomical relation between the placenta, the myometrium, the cervical vessels and the placental alos.[7] The diagnosis of amniotic fluid embolism remains clinical. No specific diagnostic laboratory tests to date have been able to rule out or confirm the definitive diagnosis of the disease.[8] The definitive diagnosis of amniotic fluid embolism is made mainly at necropsy by confirming the presence of fetal material in the pulmonary circulation or in a surviving patient in bronchial lavage with special Nile, or Wright or Papanikolaou stains.[9]

THERAPEUTIC APPROACH
Treatment of amniotic fluid embolism should initially be supportive and focus on rapid stabilization of the cardiorespiratory system and adequate oxygenation of vital organs (Table 4). Knowledge of the changes that characterize normally developing pregnancies and an understanding of how clinical practice is adapted are essential for the care of the pregnant woman in the emergency department.[10] There is no specific treatment to date.[11] The application of the treatment in a large hospital unit is estimated to have a better prognostic effect for both the mother and the fetus-newborn.[12] Thus, since amniotic fluid embolism is usually seen with cardiac arrest, the initial immediate response should focus on providing high quality cardiopulmonary resuscitation.[13] The key to treating the syndrome is immediate recognition, a high rate of clinical suspicion, immediate recovery and delivery of the fetus. Early recognition is critical to achieving the desired result. In the past, the first actions were limited to the use of morphine, atropine and oxygen. Current management focuses on oxygenation, maintenance of cardiac output, control of bleeding, and correction of blood clotting.[14,15]

RESPIRATORY SUPPORT
The sudden onset of the of heart disease with no apparent cause, the lack of specific diagnostic tests, and the complex treatment required, including cardiopulmonary resuscitation, make amniotic fluid embolism an interdisciplinary challenge to date.[16] Oxygenation and control of the airway by endotracheal intubation and

administration of 100% oxygen with positive pressure ventilation to the extent permitted by the patient's hemodynamic status should be performed as soon as possible to improve oxygenation.[17,18] Esophageal echocardiography is recommended as soon as possible, as it is an easy and reliable method that can guide fluid therapy by assessing left ventricular filling. Also, the application of arterial line and pulmonary catheter is estimated to be able to greatly assist in the guidance of treatment.[19]

In case of failure of the manipulations, the extracorporeal membrane oxygenation and the continuous venous hemodialysis can be valuable treatments. In vitro therapies can support severely ill women affected by amniotic fluid embolism in the presence of diffuse intravascular coagulation and bleeding.[20] Developments in recent years in the treatment of acute cardiopulmonary disease with venous-arterial extracorporeal membrane oxygenation have led to the view that the method can be considered a vital option for the treatment of high-risk cardiopulmonary failure. Especially in patients who do not have chronic diseases / comorbidities, early use of venous - arterial membrane oxygenation can reduce cardiac output and adequately oxygenate the patient until the transient acute anaphylactoid phase of the disease process is over.[21,22] In the event of cardiac arrest or cardiac arrhythmia, performing an emergency caesarean section, if possible within 3 to 5 minutes, is imperative.[23]

CIRCULATION SUPPORT

In addition to respiratory support, hemodynamic support for these patients with prudent use of fluids, vasoconstrictors, inotropic and pulmonary vasodilators is estimated to be vital, as it is commonly accepted that early diagnosis and aggressive treatment significantly improve prognosis and prognosis. Regarding the morbidities that are expected to appear in the future.[24] Providing immediate high-quality cardiopulmonary resuscitation with standard basic life support and advanced cardiac circulation support protocols to patients developing amniotic fluid-associated cardiac arrest is an immediate and urgent need. The administration of crystalline solutions for the treatment of hypotension and hemodynamic instability in patients should be started immediately and with a recommendation to avoid excessive fluid intake, as it may cause worsening of right ventricular failure and pulmonary edema.[25.26] Optimal tumor management is important, although it is difficult to strike the right balance between maintaining cardiac output and preventing fluid overload and pulmonary edema.[27] In those cases where hypotension and hemodynamic instability cannot be treated with the administration of fluids, the administration of vasoconstrictor therapy is required. Intravenous administration of dopamine and inotropic substances is indicated based on hemodynamic parameters, in order to maintain systolic blood pressure at levels greater than 90 mmHg.[28] It is currently estimated that dobutamine administered by intravenous pump at a dose of 2.5- 5.0 μg/kg per minute and milinone administered by intravenous pump at a dose of 0.25- 0.75 μg/kg per minute could lead to pulmonary vasodilation and be the first choise for the therapeutic approach to amniotic fluid embolism.[29, 16] Recently, nebulizer administration of milrinone, in an effort to reduce pulmonary vascular resistance to manage right ventricular failure, has been shown to reduce pulmonary vasoconstriction if used directly, providing a bridge for extracorporeal oxygenation[30] with Similarly, inhaled or intravenous prostacyclin and inhaled nitric oxide are other specific interventions aimed at reducing pulmonary vascular resistance.[25,31] In addition to respiratory support, hemodynamic support for these patients with prudent use of fluids, vasoconstrictors, inotropic and pulmonary vasodilators is estimated to be vital, as it is commonly accepted that early diagnosis and aggressive treatment significantly improve prognosis and prognosis. Regarding the morbidities that are expected to appear in the future.[24] Providing immediate high-quality cardiopulmonary resuscitation with standard basic life support and advanced cardiac circulation support protocols to patients developing amniotic fluid-associated cardiac arrest is an immediate and urgent need. The administration of crystalline solutions for the treatment of hypotension and hemodynamic instability in patients should be started immediately and with a recommendation to avoid excessive fluid intake, as it may cause worsening of right ventricular failure and pulmonary edema.[25.26] Optimal tumor management is important, although it is difficult to strike the right balance between maintaining cardiac output and preventing fluid overload and pulmonary edema.[27] In those cases where hypotension and hemodynamic instability cannot be treated with the administration of fluids, the administration of vasoconstrictor therapy is required. Intravenous administration of dopamine and inotropic substances is indicated based on hemodynamic parameters, in order to maintain systolic blood pressure at levels greater than 90 mmHg.[28] It is currently estimated that dobutamine administered by intravenous pump at a dose of 2.5- 5.0 μg/kg per minute and milinone administered by intravenous pump at a dose of 0.25- 0.75 μg/kg per minute could lead to pulmonary vasodilation and be the first choise for the therapeutic approach to amniotic fluid embolism.[29,16] Recently, nebulizer administration of milrinone, in an effort to reduce pulmonary vascular resistance to manage right ventricular failure, has been shown to reduce pulmonary vasoconstriction if used directly, providing a bridge for extracorporeal oxygenation[30] with Similarly, inhaled or intravenous prostacyclin and inhaled nitric oxide are other specific interventions aimed at reducing pulmonary vascular resistance.[25,31] In addition to respiratory support, hemodynamic support for these patients with prudent use of fluids, vasoconstrictors, inotropic and pulmonary vasodilators is estimated to be vital, as it is commonly accepted that early diagnosis and aggressive treatment significantly improve prognosis and prognosis.

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Recent promising treatments include selective pulmonary vasodilators and recombinant activated factor VIIa. Also, in patients who do not meet the support measures and there is right ventricular failure and pulmonary hypertension, the choice of sodium bicarbonate should be seriously considered, the use of which can lead to immediate normalization of cardiac parameters.[17,32] Also, the successful treatment of a patient with amniotic fluid embolism after the administration of Atropine, Ondansetron and Ketorolac regimen has been described in the literature. The newly described treatment regimen, although it does not meet the new criteria proposed by Clark in 2016, is cited by the authors as a significant attempt to treat patients with a dramatic response to the supportive care provided.[33] Finally, the use of glucocorticoids is still under discussion. Early administration of large doses of glucocorticoids can be an effective effort based on experience in clinical practice.[34]

Treatment of Disseminated Intravascular Coagulation

Correction of blood clotting disorders, after treatment of hypoxia, hypotension and vaginal delivery or by caesarean section is imperative and vital to support the patient.[35] Disseminated intravascular coagulation that can occur after severe bleeding and uterine atony after childbirth concerns a percentage of up to 83% of cases of amniotic fluid embolism.[36] Postpartum hemorrhage and disseminated intravascular coagulation caused by amniotic fluid embolism should be actively treated with early transfusion of blood products according to standard mass transfusion protocols and coagulation factors (fresh frozen plasma, fibrinogen, platelets).[37] In any case of suspected amniotic fluid embolism, immediate determination of the fibrinogen level is required in order to assess the degree of coagulation disorder. Immediate treatment of coagulation is estimated to help reduce maternal mortality from amniotic fluid embolism.[38]

Disseminated intravascular coagulation associated with bleeding is treated depending on the degree of bleeding. Disruption of the coagulation mechanism in amniotic fluid embolism, which is established in an extremely short period of time, is not directly proportional to bleeding. Transfusion with red blood cells and platelets, for those cases that thrombocytopenia is considered necessary.[39]

The administration of red blood cells and fresh frozen plasma should be based on blood loss, the severity of the bleeding, and the patient's risk profile. Tumor overload factor should be considered to avoid the risk of pulmonary edema in these patients. In any case, knowledge simulation and familiarization with a Massive Obstetric Transfusion protocol is able to help all members of the perinatal group recognize and respond to women with amniotic fluid embolism in timely and effective manner.[4] Recently, a protocol for the treatment of these patients with early use of tranexamic acid, transfusion of red blood cells and fresh frozen plasma with the addition of fibrinogen in case of hemostasis is not easily achieved.[40] Also, the use of recombinant factor VIIa should be only be considered if massive coagulation factor replacement is not sufficient to improve hemostasis and stop bleeding.[41]

The clinical controversy surrounding the use of heparin in treatment of disseminated intravascular coagulation caused by amniotic fluid embolism is intense. Heparin treatment is not recommended unless there is evidence of early hypercoagulability.[42,43,25] For many of the researchers who have dealt specifically with the subject anticoagulant therapy is the most important strategy to inhibit excessive coagulation cataract activation in patients with amniotic fluid embolism and disseminated intravascular coagulation. Oral therapy with rivaroxaban, a novel anticoagulant and selective direct inhibitor of factor Xa, has not yet been established in the treatment of these patients. Individual published cases in the literature

have shown good therapeutic efficacy of the drug in the treatment of patients with amniotic fluid embolism and disseminated intravascular coagulation. Based on these and the positive results of major trials and strong guidelines, rivaroxaban should be considered as the first preferred anticoagulant therapy for the majority of patients.[44,45]

Continued uterine bleeding (uterine atony) which is common in patients with amniotic fluid embolism when not responding to uterine contraceptives such as oxytocin, ergometrine and prostaglandins[46] may require invasive techniques for controlling bleeding (uterine plug, B-Lynch sutures) or performing obstetric hysterectomy in case they fail.[34,41] Experts today recommend vigilance for the diagnosis of amniotic fluid embolism at an early stage and the immediate execution of obstetric hysterectomy without delay for those cases of uterine atony where the bleeding is intense, persistent and resistant to medication.[47,48]

PREGNANCY MANAGEMENT

Trying to complete the delivery in the safest way for the mother and always thinking into account the condition of the fetus should be a priority in the treatment of pregnant women with amniotic fluid embolism. Obstetric emergencies, including amniotic fluid embolism, are a challenge in daily clinical practice, both for obstetricians and the anesthesiologist team.[49] Although the primary responsibility of the physician is to ensure the health and life of the mother, intervention to save the fetus is considered appropriate in some cases. Continous monitoring of the fetus is mandatory in pregnancies longer than 24 weeks. In cases of maternal heart failure, immediate caesarean section is recommended.[50] Given that brain damage begins within 5 minutes of anoxia and therefore the post-mortem caesarean section must be completed within 4 minutes (the 4-minute rule) in order to improve the perinatal outcome and possibly the outcome of maternal health.[51] The publication of the results of a twenty-year study (1985-2004) is far from proving that postmortem caesarean section within 4 minutes of maternal cardiac arrest in the third trimester of pregnancy improves maternal and neonatal outcome.[52] According to current guidelines, post-mortem caesarean section should be included in the pregnant woman after 5 minutes of unsuccessful cardiopulmonary resuscitation and if completed in time it is estimated that it could possibly help save the fetus and mother's critical resuscitation.[53]

PREVENTION

To prevent amniotic fluid embolism, it is important to optimize obstetric bleeding management procedures, especially during vaginal delivery and caesarean section. Avoiding injuries to the cervix and body of the uterus during medical procedures and avoiding injuries to the placenta during caesarean section could significantly help prevent the syndrome with all the devastating complications it can have for mother and newborn. Similarly laborious vaginal delivery and tetanic uterine contractions should be treated with appropriate treatment, while the use of oxytocin should be done with great caution and only when deemed medically necessary.[54]

Also, the care for the early recognition of the precursor symptoms and signs of amniotic fluid embolism by health professionals seems to be crucial. Reports from the patient, such as shortness of breath, chest pain, cold, anxiety, panic, nausea and vomiting, should in any case be taken seriously and evaluated accurately in order to achieve early diagnosis of the disease and the most effective treatment.[55] Early diagnosis and treatment are crucial for the survival of both the pregnant woman and the fetus-newborn.[56] Acute renal failure, acute respiratory distress syndrome, hypoxic-ischemic brain injury, and severe sepsis are very likely to occur even after a successful first resuscitation of the patient with amniotic fluid embolism.[57]

CONCLUSION

Amniotic fluid embolism is a catastrophic obstetric complication that requires timely and aggressive intervention with optimal cardiopulmonary resuscitation, as well as immediate management of bleeding and coagulation. The prognosis of the mother after amniotic fluid embolism is very poor although the survival rate of infants is about 70%.[58] The continuation of the research effort is expected in the future to shed light on important and crucial aspects of the obstetric problem and to significantly improve perinatal and maternal mortality. It is expected that limiting research on amniotic fluid embolism to women who meet the criteria of the classic trinity will enhance the validity of published data and help identify risk factors and potentially useful biomarkers for early diagnosis and effective treatment.[59]

TABLES

Table 1: Basic principles of treatment of pregnant women with amniotic fluid embolism.

- **Breathing support**

-endotracheal intubation
-oxygenation

- **Traffic support**

-administration of crystalline solutions
-dopamine administration
-administration of inotropic substances
-administration of sodium bicarbonate

- **Treatment of diffuse intravascular coagulation**

-red blood cell transfusion
-plasma transfusion
-platelet transfusion
-administration of anticoagulant therapy
-administration of rivaroxaban?
-obstetric hysterectomy

- **Pregnancy management**

-fetal monitoring.
-caesarean section.
-post-mortem caesarean section.

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