Embolism during pregnancy: thrombus, air, and amniotic fluid

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Since 1985, embolism has been the predominant cause of maternal deaths (20%) in the United States, outscoring the number of deaths caused by hypertensive disorders, obstetric hemorrhage, obstetric infection, and ectopic pregnancies [1]. A similar trend has been observed in other developed countries [2–5].

Embolic diseases are the commonest cause of an acute hemodynamic and respiratory collapse during pregnancy. The accidental or inadvertent entry of solids (foreign bodies), gas (air, CO_2), or liquids (amniotic fluid, fat) into the intravascular system has common physiologic implications. Given the progressive anatomic reduction of the caliber of the vessels beyond the right ventricle, regardless of the size and nature of the venous embolism, these foreign masses will become lodged in the pulmonary vascular bed at different and usually multiple levels. The ensuing obstruction of the pulmonary vasculature leads to acute ventilation/perfusion (V/Q) mismatch and a decrease in the amount and quality of oxygenated blood reaching the left side of the heart. Myocardial dysfunction, frequently seen in these patients, worsens this hemodynamic insult.

The clinical picture of embolism can range from an asymptomatic to sometimes a life-threatening emergency. The purpose of this article is to review the incidence and mortality, risk factors, common clinical presentations, diagnostic criteria, and management goals that need to be implemented rapidly to ensure the safety of parturient presenting with an embolic phenomenon.

Venous thromboembolism

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a complex disease that results from multiple interactions between inherited and acquired risk factors [6]. The identification of these risk factors, particularly the inherited causes of thrombosis, is a rapidly evolving area of molecular biology that is beyond the scope of this article.

Incidence and mortality

Pregnancy is associated with a five- to tenfold increase in the risk of VTE [6,7]. This risk is further increased during last 3 months of pregnancy, although one series documented an even distribution of thrombotic events throughout gestation [8]. Venous thrombosis occurs with a frequency of 0.5 to 2 per thousand pregnancies [9]. The relative risk of VTE during the first six postpartum weeks can be 10 to 20 times higher than that during pregnancy [6,10,11]. When untreated, up to 24% of pregnant women with DVT will develop PE, with a subsequent mortality

of 15% [2]. The recurrence of PE with subsequent pregnancies is 4 to 15%, high enough to warrant thromboprophylaxis [10,12].

The explanation for this increased susceptibility during pregnancy lies in the interaction of mechanical and biochemical physiologic adaptations. These adaptations result in the presence of all components of Virchow's triad: venous stasis (aortocaval compression), hypercoagulability (increased levels of factors II, VII, VIII, and X), and damage to the vessel wall (during vaginal and operative delivery).

Risk factors and timing during pregnancy

Risk factors for thromboembolism during pregnancy and puerperium include: maternal age greater than 35 years, higher parity, obesity, prolonged immobilization, pelvic trauma, surgery during pregnancy (including cesarean section), personal or family history of VTE, hereditary thrombophilia, multiple pregnancy, and pre-eclampsia [6,10,11,13]. A risk stratification for postpartum VTE associated with cesarean section has been proposed by Farrell [10]. It defines three groups: (1) low risk:<35 years of age, uncomplicated pregnancy, and elective cesarean section, (2) moderate risk: >35 years, obesity, gross varicose veins, recurrent infections, immobility >4 days before delivery, pre-eclampsia, and emergency cesarean section, and (3) high risk: three or more moderate risk factors, hereditary thrombophilic disease or antiphospholipid antibody syndrome, personal or family history of DVT, history of PE, and cesarean hysterectomy.

Clinical manifestations

The most common symptoms suggestive of PE are the sudden onset of dyspnea and tachypnea. Apprehension, pleuritic chest pain, nonproductive cough, and sensation of imminent death are also common [13]. Symptoms are absent in up to 70% of patients with documented PE [14]. Clinical signs that suggest PE are tachypnea, tachycardia, and arterial oxygen desaturation [13]. Laboratory findings include hypoxemia, respiratory alkalosis, and a normal chest X ray [13]. EKG findings are nonspecific and help rule out cardiac ischemia or acute infarction. Fetal heart rate monitoring usually shows several abnormalities and signs of fetal compromise [15].

Diagnosis

The clinical findings may be typical or suspicious enough to warrant starting anticoagulation treatment while awaiting the results of more specific diagnostic testing (V/Q scan, magnetic resonance angiography, spiral computed tomographic pulmonary angiography or pulmonary angiography). Up to 60% of V/Q scans are classified as intermediate or indeterminate probability, and the risk of PE in this situation is 20%. A pulmonary angiogram is required either in patients who have a negative V/Q scan but strong clinical suspicion for PE or in severe cases for confirmation of PE before selective thrombolysis. The radiation dose to the fetus is inconsequential and has been estimated at 0.5 rad with combination chest X ray, V/Q scan, and pulmonary angiography [10].

During pregnancy, the source of VTE can almost always be traced to the veins in pelvis or lower extremities, where venous return is compromised by compression of the gravid uterus on the iliac veins. The left lower extremity is affected 85% to 90% of the time as the aorta crosses the left common iliac vein [9,10,16]. Maternal thrombosis occurs more frequently in the iliofemoral (up to 72%) than in calf veins (9%) [16]. During the postpartum period, up to 50% of the deep thromboses occur in the popliteal area [10]. Physical examination can be helpful in the presumptive diagnosis of embolism if the physical findings are positive. Nevertheless, most venous thrombi are clinically silent, and fewer than 30% of patients present with the triad of edema, calf discomfort, and pain on dorsiflexion [2].

Symptomatic thrombosis of the thigh should be assessed initially by Doppler ultrasound. Recently, MRI, using gradient recalled sequences, has been shown to be an accurate method of assessment for pelvic and lower extremity vessels [9]. This test is particularly useful when the suspected vessels are pelvic and beyond the access of Doppler ultrasound and venous plethysmography. Another indication for MRI is to evaluate possible propagation of the clot in the patient with a pre-existing thrombus who fails to improve with treatment.

When other tests are nondiagnostic and the suspicion of calf thrombosis is high, venography may be indicated; in this case the pelvis should be shielded and the test limited to the calf [10]. Venography is not without complications (including venous thrombosis) and so is not the technique of choice in pregnant women.

Identification of the cause of the emboli

Since 1965, several abnormalities have been recognized that may cause hyperactivity of the coagulation system and subsequent thromboses. Thombophilia is the term used to describe these hypercoagulable states, most of which (60%)

are genetic [17]. Pregnant women who develop a thromboembolic episode should be evaluated for thrombophilia, because it is estimated that 50% of the patients with thrombophilia will develop the first thrombotic event in the presence of an additional risk factor, such as pregnancy. The relative risk of thrombotic events during pregnancy occurring with the most common of these disorders is shown in Table 1. The workup differs during pregnancy and should be performed remote from the thrombotic event and treatment with heparin or other anticoagulants [18].

Table 1. Risk of thrombotic event according to inherited defect

Defect	Frequency/Lifetime prevalence of DVT/PE	Risk of DVT/PE in pregnancy
Controls	N/A	1.0-fold/ 1.0-fold
Factor V Leiden	5%–9%	30% / 50-fold
Antithrombin III deficiency	0.2%–0.02%	70%–90% / >250-fold
Protein C deficiency	0.2%–0.5%	50% / 100-fold
Protein S deficiency	0.08%	50% / 90-fold

Data from Lockwood CJ. Heritable coagulopathies in pregnancy. Obstet Gynecol Surv 1999; 54:754–65.

Treatment

treatment of VTE during pregnancy can be divided into supportive and specific therapy

Supportive measures, in patients who develop PE, are aimed at improving and preserving adequate oxygenation and circulation. Resuscitation takes priority over any diagnostic or other therapeutic measures. Oxygen administration and cardio-respiratory support with fluids, inotropes, and vasopressors may be required and are the mainstay of the initial treatment. Patients in pain should receive analgesia, but opiates should be used with caution in a hypotensive patient. If hypoxemia is refractory to oxygen supplementation by face mask, intubation and mechanical ventilation may be necessary. This may worsen cardiac output by decreasing venous return. Right atrial filling pressure should be maintained at a high level (15 mm Hg) to maintain output from the failing right ventricle [19].

In the absence of circulatory failure, routine monitoring is sufficient. A central venous line is helpful for monitoring and as intravenous access in patients with hemodynamic compromise or shock that is refractory to initial treatment. A pulmonary artery catheter may be required if inotropes are used or if conventional monitoring is insufficient to guide the patient's treatment.

Specific measures aim to limit the damage of the material embolized and prevent the expansion or further embolization of other thrombi

Anticoagulation with unfractionated heparin (UH) remains the specific therapy of choice. An intravenous bolus of 7500 to 10,000 IU is given, followed by an infusion of 1200 to 1300 unit per hour to achieve an activated partial thromboplastin time (aPTT) of 1.5 to 2 times the upper level of laboratory control values (nomogram is shown in Table 2) [20] for 10 to 14 days. This is followed by subcutaneous injections of 5000 to 10,000 IU every 8 to 12 hours, throughout pregnancy. Heparin is discontinued shortly before delivery, and restarted postpartum in conjunction with warfarin [10,16,21]. Heparin is subsequently discontinued when the International Normalized Ratio (INR) is between two and three [16]. It is important to remember that heparin constitutes secondary prevention, as it does not dissolve the thrombi or emboli already formed. Heparin stops the formation and growth of the existing clots, decreasing the morbidity and mortality from pulmonary embolism. Heparin also reduces the bronchoconstriction and pulmonary vasoconstriction induced by thrombin and platelet activation [19].

Table 2. Weight and aPTT based heparin-dosing nomogram

Initial dose / Bolus 80 U/kg, then infusion 18 U/kg/h	
aPTT <35 s (<1.2 X control)	Bolus 80 U/kg, increase infusion by 4 U/kg/h
aPTT 35–45 s (1.2–1.5 X control)	Bolus 40 U/kg, increase infusion by 2 U/kg/h
aPTT 46–70 s (1.5–2.3 X control)	No change
aPTT 71–90 s (2.3–3 X control)	Decrease infusion rate by 2 U/kg/h
aPTT > 90 s (> 3X control)	Hold infusion for 1 hour, then decrease rate by 3 U/kg/h

aPTT is measured 6 hours after change of dosage and at least once daily. A heparin dose greater than 40,000 U/day should not be administered unless a heparin concentration of <0.2 U/mL is confirmed.

Data from Raschke et al. The effectiveness of implementing the weight-based heparin nomogram and practice guideline. Arch Intern Med 1996;156:1645–9.

Thrombolysis

The use of streptokinase (or urokinase) and r-tPA has been reported during pregnancy [5,22]. Once the woman is adequately anticoagulated, this modality of treatment should be considered if the patient has a recurrent episode of embolism. Although experience is limited, it would seem that r-tPA is a better alternative for thrombolysis as it can be administered in a shorter period of time (2 hours), has a

lower risk for allergic reactions, and may potentially have a lower risk of hemorrhage than streptokinase [5].

Low molecular weight heparin

The smaller chemical structure of this polysaccharide gives it several advantages over UH; among them a prolonged serum half life, decreased daily dosing, lower protein binding, predictable and prolonged serum clearance, lower risk of bleeding, and lower risk of platelet activation and thrombocytopenia [2].

Embolectomy is rarely indicated during pregnancy

Anesthesia in the anticoagulated patient

The issues of anesthetic options, anticoagulation reversal and regional anesthesia in the pregnant woman receiving anticoagulation therapy are reviewed in detail in another article in this issue. (See article by Abramovitz and Beilin).

Venous air embolism

History

Venous air embolism (VAE), the entrapment of air in the venous system, results in the obstruction of pulmonary arterial blood flow [13]. Amussat in France was the first to recognize the accidental entry of air into the venous system, although there had been sporadic reports of gas embolism since ancient times [23]. Legallois first suggested that it posed a potential danger in pregnancy in 1829 [24]. In 1850 Cormack published the first report of VAE in the obstetric population [23].

Incidence and mortality

The exact incidence of clinically significant VAE is unknown and is possibly underestimated. Venous air embolism is probably the most common embolic event to occur during the intraoperative period [25], and air can be demonstrated by precordial Doppler auscultation in up to 50% of cesarean deliveries [25–27]. More sensitive techniques have demonstrated VAE in 93 to 100% of patients undergoing cesarean section under general anesthesia [27]. It is obvious that significant VAE

occurs only in a small fraction of these cases. Some authors believe that the hypoxemic episodes frequently seen during cesarean section might be the result of small VAEs [28]. Even so, VAE is responsible for only about 1% of maternal deaths for a rate of approximately one death per 100,000 live births [1,24].

Risk factors

Most cases of VAE are associated with clear risk factors. Theoretically, a gradient as small as -5 cm H20 between the periphery and the heart would allow significant entry of air into the venous circulation. Trendelenburg position and exteriorizing the uterus during cesarean section increase this gradient [13]. Most VAEs that occur during cesarean delivery are detected between the time of delivery of the infant and closure of the hysterotomy incision [27]. Uterine exteriorization is thought to predispose to VAE by two mechanisms: (1) increasing the hydrostatic gradient by raising the incisional area above the level of the heart, and (2) by the simultaneous enlargement of the uterine sinuses providing more exposure to air [26].

Sexual activity during pregnancy and puerperium, including forceful air insufflation during oral sex!!! , is a well-known risk factor for VAE [26,29,30]. Pelvic venous congestion and the larger capacity of the vagina during pregnancy are considered factors in the increased number of cases reported in pregnant women compared to nonpregnant women [31,32]. Rare causes of air embolism include uterine rupture, trauma, and diving [33].

The major cause of death from VAE is circulatory arrest resulting from air entrapped in the right ventricular outflow tract. Once air is introduced into the venous system, injury can occur by three mechanisms. Because air is compressible, the froth resulting from the mix of air and blood cannot be pumped effectively. Five mL/kg of air may be lethal by formation of an “air-lock” in the right ventricle or in the pulmonary arterial circulation [29]. The resultant electromechanical dissociation results in cardiogenic shock and an acute rise in preload. In combination with pulmonary artery vasoconstriction, this phenomenon can result in acute cor pulmonale.

Increased capillary permeability, platelet activation, and coagulopathy may result from the effect of air on endothelial surfaces [31]. In addition, the interaction of air bubbles and blood products, particularly platelets, may cause the release of a variety of vasoactive substances leading to local vasospasm, activation of the coagulation cascade, and microthrombi [32].

Infrequently, air may enter the arterial circulation through a persistent shunt (paradoxical embolism), leading to end-organ perfusion damage. It is estimated that a quarter of adults have a patent ductus arteriosus and an even smaller percentage have an unrecognized atrial septal defect or a patent foramen ovale [34]. Cerebral and myocardial ischemia can result from embolization of the cerebral (vessels 30 to 60 É m) or coronary circulation respectively [32].

Clinical manifestations

The presentation of VAE is highly variable and will depend on the nature, volume, and speed of the gas introduced, the patient's size and position, and their baseline condition before the insult. As with other forms of significant embolism, suspicion of VAE may be aroused by the development of acute cardiorespiratory failure or neurological symptoms in an otherwise healthy patient, usually during or after a procedure. If the patient is awake, the symptoms of air embolism are nonspecific and include dyspnea, chest pain, restlessness, diaphoresis, and a feeling of impending death. Chest pain and dyspnea, particularly at the time of hysterotomy, develop in about two thirds of patients who have Doppler changes consistent with air embolism and should alert the anesthesiologist to this complication [23,25,32]. Signs of air embolism include tachycardia, tachypnea, cyanosis or pallor, mottled skin, pallor of mucous membranes (Liebermeister's sign when the pale areas are seen in the tongue), and blanching of arteriole segments in nail beds. Some patients exhibit a “wheel-mill” murmur, which can be detected by a stethoscope [23]. Occasionally, air bubbles can be seen on funduscopic exam [23]. Fortunately, it would appear that in most cases of VAE, the amount of air entering the venous system is small, causing no symptoms or only mild discomfort.

Diagnosis

The diagnosis of VAE may be difficult, and a high index of suspicion is required. A significant VAE commonly presents as cardiorespiratory collapse with hypotension and hypoxemia during a surgical intervention. One of the most sensitive monitors for the early detection of VAE is the end-tidal carbon dioxide (EtCO2) concentration. A sharp decline in EtCO2, accompanied by a decrease in peripheral oxygen saturation, is noted in cases of VAE with significant V/Q mismatch. The decline in EtCO2 is more sensitive than the precordial Doppler and is readily available in most operating rooms [23]. Probably the most sensitive test is transesophageal echocardiography, visualizing as little as 0.2 mL of injected air entrapped within the right atrium or ventricle.

Treatment

Immediate measures are aimed at stabilizing the patient and preventing further embolism. Communication between the anesthesia and the obstetric teams are paramount to coordinate efforts and preserve the patient's integrity. The patient needs to be positioned such that the surgical site is below the level of the heart. In obstetric patients, a semi-Fowler position may prevent further air embolism. Leftward tilt will favor the forward movement of intracardiac air bubbles into the distal pulmonary artery and pulmonary vasculature. If the patient develops any neurological symptoms and a cerebral embolus is suspected, the position of the head needs to be lowered, preserving the left lateral recumbent position in order to prevent further migration of air into the brain [32].

The surgical field must be flooded with normal saline to cover open venous sinuses. Adequate ventilation will promote the removal of small emboli by dispersion into the pulmonary vasculature. If the patient is receiving nitrous oxide, the gas should be discontinued immediately. Nitrous oxide is more soluble in blood than nitrogen and will diffuse into the air bubbles enlarging their size. Oxygen administered at an FiO2 of 1.0 improves oxygenation and decreases the size of the bubbles. Intravenous fluids need to be administered in large amounts to increase right ventricular preload in an effort to displace the bubbles into the pulmonary vasculature. Inotropes may be required to increase myocardial contractility when an increase in preload fails to increase cardiac output. Aspiration of air from the right atrium, with a multiple orifice catheter, may retrieve up to 50% of the trapped air, allowing forward blood flow and reversing a seemingly fatal outcome.

The only definitive treatment for air embolism is the administration of hyperbaric oxygen as soon as possible after the event. Hyperbaric oxygen treatment compresses the air bubble size, hopefully, to a point at which perfusion pressure can force the intravascular gas through the capillary beds and re-establish the circulation. The decrease of bubble size is directly proportional to the absolute atmospheric pressure (therefore a Gerow bag should work-i.e., increasing pressure not necessarily with 100% O2) of the treatment (Boyle's law PV=K, i.e. at a constant temperature, the volume of a gas is inverly proportional to its pressure and vice versa) [7]. Hyperbaric oxygen is especially beneficial in patients with cerebral or cardiac symptoms (ie, arterial gas embolism) [35]. This therapy should be instituted within 5 hours because a delay of treatment will result in a decreased chance of recovery. Typically, therapy with hyperbaric oxygen entails immediate treatment at 2.5 to 3.0 atmospheres for 2 to 4 hours [35]. In addition, hyperbaric oxygen increases the oxygenation of hypoxic brain tissue and reduces brain edema by decreasing cerebral blood flow and lowering hyperemia [32].

Amniotic fluid embolism

History

In the 1920s, Ricardo Meyer reported the presence of fetal cellular debris in the maternal circulation [36]. In 1941, Steiner and Luschbaugh described the autopsy findings of eight cases of AFE [37]. Until 1950, only 17 cases had been reported [38]. Since then more than 400 cases have been documented [39], probably as a result of an increased awareness.

Recently, the term Anaphylactoid Syndrome of Pregnancy, rather than Amniotic Fluid Embolism (AFE), has been proposed in an attempt to characterize the manifestations of this condition as a multi-systemic reaction to toxins rather than an embolic phenomenon (Fig. 1)[40,41]. The high incidence of multisystem failure tends to support this view [42].

Fig. 1. Components of amniotic fluid and their role in pathophysiology of AFE. Surfactant enhances production of leukotrienes C4 and D4. Endothelin and Prostaglandins E2 and F2Éø cause coronary vasoconstriction and negative inotropic effect. Leukotrienes induce hypertension followed by hypotension, pronounced negative inotropic effects and bronchoconstriction. IL-1 and TNF-Éø induce production of endothelin. Thromboxane A2 causes increases in coronary and pulmonary vascular resistance. Collagen and thromboplastin induce platelet activation.

Incidence and mortality

The true incidence of AFE is unknown [43]. The reported incidence ranges from 1 per 8000 to 1 in 83,000 deliveries [37,43,44]. A recent study from California reported an incidence of 1 per 20,646 deliveries [45]. It is conceivable that an increased awareness of this syndrome, rather than a true increase in incidence, is responsible for these differences [46].

It has been estimated that between 5% to 18% of all maternal deaths are due to AFE [43,44,47–49], a rate of about 7.8 to 12 deaths per million maternities [44,50]. Reported mortality rates range from 26% to as high as 86% [43,45,51]. The disparity in the figures is probably explained by dissimilar case definitions and, to a lesser degree, to improvement in the intensive care management of the affected

patients [45]. Amniotic fluid embolism constitutes the leading cause of mortality during labor and the first few postpartum hours [47,52]. Maternal death usually occurs in one of three ways: (1) sudden cardiac arrest, (2) hemorrhage due to coagulopathy, or (3) initial survival with death due to acute respiratory distress syndrome (ARDS) and multiple organ failure [43].

The first well-documented case with ultimate survival was published in 1976 [49], although a handful of surviving patients with presumptive diagnoses of AFE has been reported since 1947 [53–56].

Risk factors

The most frequently cited risk factors are advanced maternal age, multiparity (88% in some series), tumultuous labor, rupture of membranes, fetal death, trauma, uterine overdistension (multiple gestation, polyhydramnios, or fetal macrosomia), and use of uterine stimulants [37,39,43,44,47,57–61,64]. Patients are most likely to present during or shortly after labor or cesarean section [62]. Infrequently, AFE has been associated with therapeutic abortion, abdominal trauma, ruptured uterus, and amnioinfusion. These quoted risk factors are not constant and at the present time, the experts' consensus is that this condition is not preventable [41,43].

Pathophysiology

Fig. 2. Chronology and incidence of signs and symptoms of AFE. Amniotic fluid embolism seems to have a logarithmic presentation with a decreasing intensity, frequency and mortality as time elapses since the onset of symptoms. The majority of seriously affected patients will die within the first 30 to 60 minutes after the onset of symptoms (*Incidence data modified from* Morgan M. Amniotic fluid embolism. Anaesthesia 1979;34:20–32).

Clinically, the anaphylactoid reaction to AFE comprises three distinct phases (Fig. 2)[46].

The first or immediate phase occurs when the mother is initially exposed to amniotic fluid and can present as: (1) respiratory distress and cyanosis, (2) hemodynamic compromise with pulmonary edema and shock, or (3) cerebral hypoperfusion with seizures, confusion, or coma. These presentations can occur separately or in different combinations [46].

The second phase is seen in 4 to 50% of the patients that survive the acute cardiorespiratory insult and is characterized by coagulopathy and hemorrhage. In some women, this may be the first and only clinical manifestation.

In the third phase, the acute insult is over and the tissue injury (brain, lung, renal) for the most part is established. Depending upon the magnitude of the event and the maternal physiologic reserve, the patient may or may not recover from this injury. During this convalescent period, which may last weeks, affected patients may die as a consequence of the severe lung or brain injury, multi-organ failure, or because of an infection acquired in the ICU [46].

Symptoms and signs

The symptoms and signs associated with AFE are fairly vague, nonspecific, and common to other forms of embolism [37,43,44,48,51,63,64]. The combination of signs and symptoms and their temporal relationship makes the diagnosis presumptive. Respiratory distress, cyanosis, cardiovascular collapse, coma, and hemorrhage have been described as the five cardinal signs of AFE [65,66]. Hemorrhage and fetal distress may also be the presenting symptoms, sometimes preceding other manifestations. It is therefore necessary to maintain a high index of suspicion for AFE [46].

Diagnosis

In the past a definitive diagnosis was made only at autopsy, by finding epithelial squamous cells, lanugo hair, fat derived from vernix caseosa, mucin derived from infant's intestinal mucus or bile derived from meconium in the maternal pulmonary vasculature [36,37,67]. Although finding fetal remnants in the maternal circulation were thought to be specific for AFE, only 50% of patients resuscitated from AFE have these findings [41]. Various diagnostic stains (Attwood [36], Giemsa [49], Wright [68], Papanicolaou [69], or Nile Blue [56,70]) and tests (fetal isoantigen, monoclonal antibody TKH-2, Zinc coproporphyrin-1 inc) [71–73], to confirm the presence of fetal squamous cells, amorphous debris, bile containing meconium, fat from vernix caseosa, fetal gut mucin, or lanugo hair, have been described in literature, but their success in diagnosing AFE seems to be fairly limited. The interested reader is encouraged to consult these sources for different diagnostic tests [62].

Chest X ray is usually nondiagnostic and may be completely normal. The EKG may show evidence of acute right ventricular strain in early stages [68]. Lung V/Q scan

may aid in the diagnosis and show nonspecific multiple perfusion defects, a finding also seen in pulmonary thromboembolism. [13]. Echocardiography can be done at the bedside, confirming severe left ventricular failure [74]. Most of the patients are hemodynamically unstable, so it is difficult to do any specific testing or obtain the results in time to alter the management. Some authors believe that there is no diagnostic test for AFE and it is a diagnosis of exclusion [42,62].

Monitoring

To assess the effectiveness of treatment and resuscitation, it is prudent to continuously monitor EKG, SpO2, EtCO2, and urine output. There is support in literature for early placement of arterial, central venous, and pulmonary artery catheters to provide critical information and guide specific therapy [75]. Central venous pressure monitoring is important to diagnose right ventricular overload and guide fluid infusion and vasopressor therapy. Blood can also be sampled from the right heart for diagnostic purposes. Pulmonary artery and capillary wedge pressures and echocardiography are useful to guide therapy and evaluate left ventricular function and compliance. An arterial line is useful for repeated blood sampling and blood gases to evaluate the efficacy of resuscitation.

Treatment

As no specific therapy exists, the treatment of AFE is supportive and directed toward: (1) maintaining oxygenation and keeping the arterial PO2 > 60 mm Hg [76] or the hemoglobin saturation at 90% or higher [43], (2) maintaining cardiac output, systolic blood pressure≥90 mm Hg, and acceptable peripheral organ perfusion (urine output ≥ 25 mL/hour) [77], (3) correcting coagulation abnormalities [58,78,79], and (4) re-establishing uterine tone. As AFE is a rapidly lethal condition, it is imperative to institute supportive care as promptly and aggressively as the presentation of AFE itself [48,49].

Resuscitation is best performed with left uterine displacement to maintain optimum uterine perfusion [78,79]. The Trendelenburg position may improve venous return. As intubation and CPR may be required it is necessary to have easy access to the patient, experienced help, and a code cart with intubation equipment, backboard, and vasopressors.

Ventilation/oxygenation

Oxygen should be administered at concentrations of 100% [39]. Securing an airway is advisable, when oxygenation and airway patency is compromised due to seizures, shock, or severe respiratory distress [39,43]. Indications for intubation and ventilation include: apnea, PaO_2< 55 mm Hg with FiO_2 of 0.5, a rising $PaCO_2$, inability to handle the work of breathing, mental status deterioration, and hemodynamic instability. Ventilation with high-inspired FiO_2 is frequently necessary to alleviate severe hypoxia. Smaller tidal volumes (6 to 8 mL/kg body weight) minimize the impact of alveolar overdistension or barotrauma, venous return and ventilation-perfusion mismatch. Ventilation to normocapnia (30 to 32 mm Hg) and prevention of respiratory alkalosis helps to maintain uterine perfusion [21].

In patients who remain hypoxic at high FiO_2 the addition of positive end-expiratory pressure (PEEP) helps (1) to improve oxygenation in patients with large V/Q mismatch, (2) to reduce FiO_2, and (3) to reduce or prevent pulmonary edema. Commonly, PEEP is started at 5 cm H_2O and increased by 2 to 3 cm H_2O, with careful assessment of lung compliance, peak airway pressures, blood pressure, and cardiac output, until satisfactory levels of PaO_2 are reached or unacceptable hemodynamic compromise occurs [39,47,80].

Cardiovascular support

Immediate resuscitation efforts include infusion lines and optimization of preload with rapid volume infusion. The EKG helps detect and treat potentially lethal bradycardia and arrhythmias [41]. The most common cause of cardiac arrest is electromechanical dissociation (up to 50% in the first hour). In the event of cardiac arrest, advanced cardiac life support protocols have to be instituted immediately and, if the fetus is to survive, a short interval from arrest to delivery is essential [39,41]. Resuscitative measures are also more effective for mother because of lack of aortocaval compression and increased venous return [81].

In theory, epinephrine should be the drug of choice for any anaphylactoid reaction. During the early stages, direct acting vasopressors such as phenylephrine may be useful in restoring aortic perfusion pressure [62]. Once initial resuscitation with aggressive use of fluids and vasopressors is successful, the patient should be transferred to an ICU. Hemodynamic monitoring with an arterial and a central venous or a pulmonary artery catheter is often helpful to guide further fluid and pharmacologic support [58,78]. Other inotropes such as dopamine or dobutamine can be added to improve myocardial function as dictated by invasive hemodynamic monitoring.

Blood samples from a "wedged" catheter may be sent to the laboratory to assist the clinicians in confirming the clinical diagnosis [68–70,73]. Sending these samples is important when the signs and symptoms of AFE closely resemble those of pulmonary thromboembolism. Not only will a positive result dissuade clinicians from pursuing pulmonary angiography and thrombolytic therapy [82], but it also allows the anticipation of coagulopathy. Infrequently, AFE can be complicated by pulmonary thrombosis that will appear as refractory hypotension [80]. A team approach among intensivists, pulmonologists, cardiologists, hematologists, and neurologists is invaluable for optimum patient outcome.

Pharmacological treatment will be guided by the hemodynamic parameters and the clinical course. In addition to the infusion of crystalloid, it is often necessary to use inotropic drugs (rapid digitalization + beta adrenergics) [74,75,83] and vasopressors (ephedrine, dopamine, dobutamine, norepinephrine) [55,75,78]. After correction of hypotension, fluid therapy should be restricted to maintenance levels to minimize pulmonary edema with subsequent ARDS [58]. Corticosteroids (hydrocortisone 500 mg IV every 6 hours) have been suggested as potentially helpful. [47,48]. Therapeutic heparinization to limit intravascular coagulation is controversial and cannot be routinely recommended at this time [54,58,61,84,85]. Other therapeutic interventions reported anecdotally include open cardiac massage [79], epsilon-aminocaproic acid [39,47], cardiopulmonary bypass [80], cryoprecipitate [86,87], inhaled prostacyclin [88], inhaled nitric oxide [89], exchange transfusion [90], prostaglandin inhibitors [51,91], antithrombin III [44], serine proteinase inhibitor [92], and leukotriene blocking agents (5-lipo-oxygenase inhibitor) [93]. In cases of severe left ventricular dysfunction, mechanical hemodynamic support (intra-aortic balloon pump) can be considered [52].

In the near future some of these agents may conceivably play a role in the management of this condition but, at present, no specific recommendations can be made for any of these therapies. In rare instances, cardiopulmonary bypass and pulmonary thromboembolectomy have been used successfully in cases of refractory hypotension [94].

Coagulopathy/hemorrhage

Treatment of the bleeding diathesis in AFE is difficult and should be guided by the coagulation profile and the hematologist [51]. Administer fresh whole blood or packed red blood cells, fresh frozen plasma, cryoprecipitate, and platelets, as needed, to maintain organ perfusion, adequate coagulation factors, and urinary output and until bleeding secondary to disseminated intravascular coagulation

resolves [43,49]. There are no absolute transfusion thresholds or factor concentrations on which to base blood replacement [62].

It has been suggested that cryoprecipitate may be useful in cases when conventional therapy appears to be unsuccessful in maintaining blood pressure, oxygenation and hemostasis [62]. Cryoprecipitate is rich in both fibrinogen and fibronectin, the latter facilitating the uptake and filtration of antigenic cellular, toxic, and particulate debris (eg, amniotic fluid contents) from the blood via the reticuloendothelial system [77,86]. When transfusing blood products, remember that the shock seen in these patients is out of proportion to the amount of bleeding and that vasopressors are an indicated adjunct to blood replacement [55].

Restoration of uterine tone

Uterine atony is best treated with massage, uterine packing, and oxytocin or prostaglandin analogues [39]. Improvement in cardiac output and uterine perfusion helps restore uterine tone. Extreme care should be exercised when using prostaglandin analogues in hypoxic patients [44], as bronchospasm may worsen the situation.

In patients with any evidence of coagulopathy, either clinical (bleeding around catheter or any other site) or diagnostic (evidence of disseminated intravascular coagulation), it is prudent to leave the epidural catheter in situ until the coagulation profile returns to normal. After removal of the catheter, the patient should be monitored closely for any signs of an epidural hematoma [76].

Summary

Pulmonary embolism is the primary cause of acute respiratory decompensation during pregnancy. Regardless of the nature of the embolism, a high index of suspicion, early diagnosis, and aggressive resuscitation need to be instituted to achieve a successful maternal and fetal outcome. Several clinical characteristics will assist practitioners to distinguish among the different forms of embolism and to institute specific measures of treatment.

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