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# Maternal Death Following Cardiopulmonary Collapse after Delivery: Amniotic Fluid Embolism or Septic Shock Due to Intrauterine Infection?

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## Abstract

**Problem—**The amniotic fluid embolism (AFE) syndrome is a catastrophic complication of pregnancy frequently associated with maternal death. The causes and mechanisms of disease responsible for this syndrome remain elusive.

**Methods of study—**We report two cases of maternal deaths attributed to AFE: 1) one woman presented with spontaneous labor at term, developed intrapartum fever, and after delivery had sudden cardiovascular collapse and disseminated intravascular coagulation(DIC), leading to death; 2) another woman presented with preterm labor and foul-smelling amniotic fluid, underwent a Cesarean section for fetal distress, and also had postpartum cardiovascular collapse and DIC, leading to death.

**Results—**Of major importance is that in both cases, the maternal plasma concentration of tumor necrosis factor (TNF)-α at the time of admission to the hospital and when patients had no clinical evidence of infection was in the lethal range (a lethal range is considered to be above 0.1 ng/mL).

**Conclusions—**We propose that subclinical intra-amniotic infection may be a cause of postpartum cardiovascular collapse and DIC and resemble AFE. Thus, some patients with the clinical diagnosis of AFE may have infection/systemic inflammation as a mechanism of disease. These observations have implications for the understanding of the mechanisms of disease of patients who develop cardiovascular collapse and DIC, frequently attributed to AFE. It may be possible to identify a subset of patients who have biochemical and immunological evidence of systemic inflammation at the time of admission, and before a catastrophic event occurs.

### Keywords

Bacteremia; cardiorespiratory arrest; chorioamnionitis; disseminated intravascular coagulation; DIC; fever; intra-amniotic infection; pregnancy; preterm labor; tumor necrosis factor-α

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## INTRODUCTION

The differential diagnosis of sudden cardiovascular collapse and disseminated intravascular coagulation (DIC) in pregnant women is a clinical challenge. This condition may occur during pregnancy or in the immediate postpartum period, and is often attributed to amniotic fluid embolism (AFE); yet, the status of AFE as a distinct entity has been debatable.[1;2] This condition has been proposed to be a syndrome[1] caused by multiple etiologies, such as an "anaphylactoid-like reaction",[3;4] emboli of particulate material from amniotic fluid,[5–7] and sepsis.[2]

We report herein two cases of maternal death following cardiopulmonary collapse after delivery. These cases are of interest for three reasons. First, both cases were associated with intrauterine infection and with plasma tumor necrosis factor (TNF)-α concentrations, which were considered to be above the lethal range.[8] Host derangements during sepsis that lead to shock, multi-system organ failure, and DIC are known to be caused by endogenous mediators produced by cells of the immune system in response to overwhelming infection.[9] However, subclinical intrauterine infections are not known to trigger similar host responses during pregnancy.

Second, at the time of the cardiopulmonary collapse, the clinical diagnosis in one patient was AFE, which was also part of the differential diagnosis in the second patient. Since subclinical intrauterine infection is not widely recognized as a cause of cardiopulmonary collapse and DIC, cases of subclinical intrauterine infection may be misdiagnosed as AFE[2] and, hence, inadequately treated.

Third, the hemodynamic changes in these patients were similar to those previously reported in some patients with AFE.[1;9–20] The parallels of the clinical and hemodynamic picture caused by subclinical intrauterine infection and AFE suggest that the same mediators[21–24] maybe implicated in the host response of these conditions.

These two cases came to our attention because they occurred during a short period of time and resulted in maternal death.

## CASE REPORTS

### Case 1

A 29-year old gravida 3, para 1 was admitted in early labor at 41 5/7 weeks' gestation. On examination, thick meconium and fetal heart rate decelerations were noted. As preparations were being made for a Cesarean delivery, the fetal heart tracing improved, an amnioinfusion was administered and the patient was allowed to continue to labor. Augmentation with oxytocin was undertaken, and an intrauterine pressure catheter was placed two hours after augmentation began. Twelve hours after admission, at a cervical dilatation of 8 centimeters, an epidural was administered. Forty minutes after the epidural was given, the patient had a temperature of 38.7°C, and blood cultures were drawn. The temperature rose to 39.2°C twenty minutes later. Shortly thereafter, the patient became fully dilated, and the fetus was delivered by vacuum extraction at 10:10 pm because of fetal heart rate decelerations. The placenta was delivered intact two minutes later.

Immediately after delivery, the patient developed a clinically progressive coagulopathy. Uterine bleeding persisted despite multiple injections of methergine and carboprost, and she began to bleed from intravenous sites and small, first degree vaginal lacerations. Within an hour after delivery, the patient developed hypotension (blood pressure 88/56), tachycardia (pulse 162), tachypnea (respiratory rate 44/min), and blood in a red top tube did not clot. At

this time, the patient's hemoglobin (Hgb) was 9.8 g/dl, white blood cell(WBC) count was 6,600 cells/μL, and the platelet count was 115,000/mL. The bleeding from the intravenous sites became profuse. Transfusions were begun at 11:40 p.m. and by midnight, the patient had received 4 units of packed red blood cells (PRBCs) and 4 units of fresh frozen plasma (FFP). Half-an-hour later the patient was intubated because of progressive respiratory failure. An arterial blood sample showed a pH 7.05, $PaO_2$ 487 mmHg, $PaCO_2$ 37 mmHg, and $HCO_3^-$ 10 mEq/L. The patient continued to be hypotensive and was started on norepinephrine and dopamine. At 2:00 a.m. (i.e., about four hours after delivery and three hours after cardio-respiratory symptoms began), the patient developed pulmonary edema confirmed by chest X-ray and furosemide was administered. A coagulation profile showed: a fibrinogen 107 g/L, a prolonged prothrombin time (PT) 18.7 secs, and an activated partial thromboplastin time (aPTT) 123 secs. The Hgb was 9.0 g/dl and the hemorrhage was abating. The patient had received 24 units of PRBCs, 23 units of FFP, 3 units of platelets, and 2 units of cryoprecipitate. The antepartum blood cultures were reported to contain Gram positive cocci growing in pairs, and the patient was started onbroad-spectrum antibiotics (ampicillin, gentamicin and clindamycin). Subsequently, the patient received metronidazole and was given intravenous hydrocortisone. Because of persistent hypotension and pulmonary edema, a Swan-Ganz catheter was placed at 4:00 a.m. Right and left heart pressures were as follows: the right arterial pressure (RAP) was 25 mmHg, pulmonary artery pressure (PAP) 35/25 mmHg, and pulmonary capillary wedge pressure (PCWP)25 mmHg. The cardiac output was 2.3 L/min. Two hourslater the chest X-ray had improved with continued diuresis. Over the next twelve hours, the patient remained hypotensive despite vasopressor and inotropic support, and had a cardiac arrest which was refractory to all resuscitative efforts. The patient was pronounced dead 19 hours after delivery. An autopsy was declined by the family. Placental histology revealed acute chorioamnionitis.

After the death of the patient, samples of blood which had been drawn for clinical care were retrieved for cytokine analysis. The blood sample had been collected at admission as part of routine care to determine a complete blood count (CBC, lavender tube collected with EDTA). Plasma TNF-α was assayed using a commercially available enzyme-linked immunosorbent assay (ELISA) (Factor Test-Human TNF-α, Genzyme Corporation, Cambridge, MA, USA). The plasma TNF-α concentration was 1 nanogram per ml.

## Case 2

A 30-year old gravida 3, para 2 was admitted in premature labor at 28 2/7 weeks' gestation. The patient had a history of asthma, two prior cesarean sections, and was allergic to erythromycin. There was no evidence of rupture of membranes (nitrazine, ferning, and pooling were negative), and the cervical dilatation was 4 centimeters with bulging membranes. The patient received two doses of Betamethasone (12 mg intramuscularly) and tocolysis with magnesium sulfate and indomethacin, which was only temporarily effective, as spontaneous rupture of membranes occurred 24 hours after admission. The amniotic fluid was foul-smelling, but the patient remained afebrile; 31.5 hours after admission the patient was delivered by Cesarean delivery under spinal anesthesia, due to a non-reassuring fetal heart tracing. Blood cultures were performed prior to delivery, and placenta, uterus and cord blood were cultured after delivery of the neonate. Cultures from the uterus were positive for *Bacteroides bivius* but the other cultures were negative. Histology of the placenta showed chorioamnionitis, funisitis and chorionic vasculitis.

In the recovery room, the patient complained of shortness of breath. The dressing over the incision was saturated with blood and vaginal bleeding was noted. The patient developed tachycardia (pulse 150) and hypotension (blood pressure 80/50). Oxygen saturation was 75% by pulse oximetry, and arterial blood gases (the patient was receiving 10 L/min of $O_2$ by face mask) were: pH 7.22; $PaO_2$ 74 mmHg; $PaCO_2$ 30 mmHg; $HCO_3^-$ 12 mEq/L; %Sat

$O_2$ 92%. Shortly afterwards the patient had a cardio-respiratory arrest. She was immediately intubated and ventilated and was successfully resuscitated. A Swan-Ganz catheter and aortic line were placed to monitor hemodynamic status.

After resuscitation, coarse rhonchi and expiratory wheezing were heard over both lungs. Chest X-rays obtained immediately before and after resuscitation showed ground glass opacities suggestive of early acute respiratory distress syndrome (ARDS). Immediately after resuscitation, arterial blood gases on 100% inspired $O_2$ were: pH 7.10; $PaO_2$ 128 mmHg; $PaCO_2$ 37 mmHg; $HCO_3^-$ 10 mEq/L; %Sat $O_2$ 97%. Initial central pressures were: mean RAP 15 mmHg, right ventricular pressure 34/6 mmHg, PAP 34/20 mmHg, PCWP 19 mmHg. The patient developed DIC, and became febrile and leukopenic. She received 8 units of PRBCs and 4 units of FFP. CBC and the coagulation profile showed: Hgb 8.1 g/dl, WBC count 2,600 cells/μL, platelet count 144,000/mL, PT 16.3 secs, aPTT 79.2 secs, fibrinogen 243 g/L, and fibrin split products >40 μg/mL.

Following resuscitation, diuresis, and inotropic support, the patient's pulmonary edema resolved and over the ensuing week her post-operative course was characterized by progressive sepsis, leukocytosis, thrombocytopenia and coagulopathy, hypotension and a hyperdynamic state. Blood cultures were positive for Gram positive cocci and Candida. The patient developed acute tubular necrosis, hepatic failure and hepatic encephalopathy. Ventilatory support with positive end-expiratory pressure (PEEP), dialysis, hemodynamic monitoring, and vigorous antibiotic therapy was continued and after one week, the patient's condition appeared to be improving. However, the improvement was short-lived and by the end of the second week of hospitalization the patient's temperature and WBC count began to rise. Signs of early pulmonary edema reappeared and the patient required increasingly higher levels of PEEP and FiO2 to maintain oxygenation. The patient died 17 days after delivery following cardiac arrest and electromechanical dissociation that was refractory to all resuscitative measures.

A plasma sample for CBC had been obtained 24 hours after admission when the membranes ruptured spontaneously and 7.5 hours prior to delivery. This sample was assayed for TNF-α as previously described and the concentration was 10 nanograms per ml.

Review of records of these two cases was approved by the Human Investigations Committee of Wayne State University, since the faculty of the School of Medicine covered the obstetrical service at Hutzel Hospital, Detroit, Michigan, where the patients were treated.

## DISCUSSION

### Principal findings

1) Two pregnant women developed cardiovascular collapse and DIC in the immediate postpartum period and eventually died. The differential diagnosis included AFE; 2) both patients had been admitted without evidence of infection or systemic inflammation. One developed an intrapartum fever after epidural anesthesia, while the other patient was afebrile but had preterm labor with foul-smelling amniotic fluid. Both patients had positive cultures for microorganisms (blood in one case and uterine in the other) and had histologic evidence of chorioamnionitis; 3) blood samples that had been obtained hours before cardiovascular collapse and DIC showed plasma concentrations of TNF-α 10 and 100 times above the lethal concentration in meningococcal sepsis; yet, the mothers were asymptomatic; 4) we propose that infection can cause a clinical picture similar to AFE, and that some cases of AFE may be due to this cause; 5) determination of cytokines at the time of admission to the hospital may help identify pregnant women at risk for cardiovascular collapse and DIC before the clinical manifestations of these complications.

## The description of amniotic fluid embolism as a unique complication of pregnancy

Although a case of AFE (maternal death in a case of stillbirth with embolic material in the lungs) was reported in 1926 by Meyer[5] in Sao Paolo, Brazil, this case published in Portuguese went unrecognized for many years. The credit for a systematic description of AFE has been attributed to Steiner and Lushbaughin 1941 in a classic paper entitled "Maternal pulmonary embolism by amniotic fluid as a cause of obstetric shock and unexpected deaths in obstetrics".[6] The authors described 8 women who died of this condition. They considered that the striking and essential pathological findings were emboli of foreign bodies (fetal material) in the blood vessels of the maternal lung. The control group consisted of 34 women who died during labor or within the first 7 days of delivery, and whose clinical presentation was not consistent with AFE. None of the 34 mothers had the embolic material in the lungs.[6]

Steiner and Lushbaugh[6] also provided experimental evidence that intravenous injection of human amniotic fluid rich in vernix or meconium into dogs and rabbits could cause a similar clinical condition as the one described in humans in the same paper. On the basis of the clinical presentation, detailed pathologic examination and experimental studies, Steiner and Lushbaugh proposed a new obstetrical disease: AFE. The association between AFE and DIC was reported in 1950 by Weiner and Reid.[25]

There has been reluctance over the years to accept AFE as a disorder because of unanswered questions about the etiology and the mechanism of disease.[1] For example, the amount of amniotic fluid debris present in the lungs has been considered insufficient by some to explain death on a mechanical basis alone.[1;26] Others found difficulty in accepting the alternative explanation favored by Steiner and Lusbaugh[7] that an "anaphylactoid-like reaction" could be responsible for the disorder. There has also been the concern that AFE could be a convenient diagnosis to attribute unexplained, sudden obstetrical death caused by other conditions such as cardiac arrest or anesthesia-related death.[1] A controversial issue has been the interpretation of experiments in which amniotic fluid has been injected into animals.[1] Several investigators have reported conflicting results. In some experiments, animals have developed a syndrome similar to AFE,[27–31] while in others, the syndrome did not develop at all.[32;33]

## Current understanding of amniotic fluid embolism

AFE typically occurs during labor and delivery or in the immediate postpartum period, although it can occur as late as 48 hours postpartum. About 70% of cases(range, 63–76%)occur before delivery and the rest in the immediate postpartum period. A minority of AFE cases occur before labor (13%). Indeed, AFE has been reported to occur following induced abortion, feticide, transabdominal amniocentesis, blunt abdominal trauma, surgical trauma and removal of a cervical suture.[20]

AFE is considered a syndrome that resembles anaphylactic and septic shock and it has been proposed that the mediators are released in response to fetal antigens.[1;2] This interpretation is based on the observations by Clark et al[2] who reported the findings collected by the National Registry of cases of AFE as well as the experimental evidence of several investigators.[3;4;34;35] The reader is referred to a recent review of AFE.[20]

## Sepsis and septic shock: complex phenotypes with different molecular pathophysiology

Severe sepsis is the leading cause of death in intensive care units, and accounts for 9.3% of all deaths in the United States per year.[36–39] Indeed, sepsis is the third leading cause of death in developed societies with mortality comparable to myocardial infarction.[37;39] It is defined by the clinical signs of a systemic inflammatory response to infection.[40;41] A

diagnosis requires evidence of bacterial infection and at least two of the following signs: 1) abnormalities of body temperature (fever or hypothermia); 2) tachycardia; 3) tachypnea; or 4) changes in the WBC count (leukocytosis or leukopenia). If the clinical process is associated with signs of organ dysfunction, sepsis is considered severe. Examples of these signs are hypoxemia, oliguria, elevated liver enzymes, lactic acidosis or altered cerebral function.[40;41] The disappointing results of clinical trials to treat sepsis have led to the realization that there is substantial phenotypic heterogeneity in this condition. Indeed, treatment with recombinant human activated protein C has been approved by the FDA only for a subset of patients with sepsis.[42]. Therefore, several leaders in the field have proposed that a distinction be made between septic shock and sepsis. Septic shock refers to a highly lethal syndrome of cardiovascular collapse that results in death within 24–48 hours after onset. It has been noted that most cases of sepsis show a more protracted clinical course in which there is multiple organ dysfunction leading to death within 7–14 days in 30–70% of the cases.[43;44] These two clinical syndromes may represent different stages of the progression of sepsis, as is the case in fulminant meningococcemia. This is important because there is an increasing realization that these syndromes are distinct disorders and represent different pathophysiologic states. The cytokine profile is different for septic shock and severe sepsis. TNF-α is the prototypic cytokine elevated in septic shock. In contrast, HMGB-1 is the typical cytokine elevated in the course of sepsis.

## Intra-amniotic infection is frequent and subclinical

There is a large body of evidence that indicates that microbial invasion of the amniotic cavity is common in women with spontaneous labor at term (the rate of positive culture is 18%), prelabor rupture of membranes at term (32%), preterm labor with intact membranes (13%), preterm PROM (32%), and cervical insufficiency (50%).[45] The use of molecular microbiologic techniques suggests that the frequency of microbial invasion may be higher than is recognized now.[46–51] However, most of the cases are subclinical in nature, and diagnosis depends upon the analysis of amniotic fluid. Even in cases of clinical chorioamnionitis (defined as originally proposed by Gibbs et al[52]), sepsis and DIC are rare. It seems that the immune system and treatment with antibiotics are able to successfully control most infections. An interesting finding of the 2 cases we report is that cardiovascular collapse and DIC occurred after delivery in patients who did not have overt clinical evidence of infection at admission to the hospital, but had TNF-α concentrations that were in the lethal range at that time.

## The role of TNF-α in sepsis

TNF-α is a primary mediator of the innate immune response to microbial invasion.[53] At low concentrations, TNF-α has been proposed to play a physiological role in maintaining homeostasis.[54] This cytokine promotes remodeling or replacement of injured or senescent tissue by stimulating fibroblast growth.[54] However, TNF-α is produced in large amounts in response to microbial products, such as endotoxin and other exogenous and endogenous factors from bacteria, viruses, and parasites.

TNF-α is a sufficient and necessary mediator of septic shock.[53] Evidence in support of this is that: 1) this cytokine produces a condition indistinguishable from septic shock when injected into animals;[55–58] 3) TNF-α is elevated in patients with septic shock;[8;56–60] and 3) the neutralization of TNF-α can prevent endotoxic or bacteremic shock, even when endotoxins and bacteremia are present in the circulation.[55] TNF-α is not a mediator of severe sepsis, as defined in the previous section. This is supported by the following observations: 1) TNF-α is almost undetectable in patients with severe sepsis;[61;62] 2) TNF-deficient knock-out mice can develop sepsis when treated with high doses of endotoxin;[63] 3) peak TNF-α production during sepsis correlates with the development of septic shock, but

not with the slow progression of severe sepsis;[56;57] 4) death from severe sepsis occurs days after TNF-α concentrations have decreased;[53] and 5) antibodies against TNF-α are either ineffective or worsen the outcome of peritonitis-induced sepsis in animals.[64;65] Thus, TNF-α participates in the initial stages of the response to infection and the generation of septic shock, but not in the progression of sepsis to death.

Given the central role of TNF-α in the inflammatory response, blocking its production or action has been widely investigated as a therapeutic strategy in conditions associated with exaggerated inflammatory response and especially in sepsis. However, randomized clinical trials of selective neutralizing antibodies against TNF-α in human subjects with sepsis did not show a significant reduction in mortality; yet, these studies included a highly heterogeneous population.[66] Nevertheless, anti-TNF-α agents are effective and in use in rheumatoid arthritis and other inflammatory diseases such as psoriasis and ankylosing spondilytis, as well as in cancer.[66;67] Recently, TNF-α inhibitors have been shown to improve pregnancy rates in women undergoing IVF and to improve birth rates in patients with recurrent spontaneous abortions.[68–71] The safety of such treatment during pregnancy is not clear.[72–75]

Several pharmacological approaches have been used to develop agents that block or modify the function TNF-α as a central regulator of inflammation, including monoclonal antibodies, soluble receptors that can bind TNF-α, and small molecules that target specific signaling and synthesis pathways for TNF-α. The different types of anti- TNF-α agents are a subject of a recent review.[66]

## TNF-α circulating concentrations

Waage et al.[9] reported that in patients with meningococcal septicemia, death occurred if the TNF serum concentrations were more than 0.1 ng/mL. Subsequent studies have demonstrated that the elevation of TNF-α is short-lived,[55;59;76;77] and that the concentrations of this cytokine over time correlate inversely with survival.[78] However, some patients with TNF-α concentrations in the “lethal range” have survived.[79]

In the two patients presented herein, plasma TNF-α concentrations were 10–100 fold higher than the concentration previously reported to be lethal in patients who have meningococcal septicemia.[9] Even more astonishing was that these concentrations of TNF-α were present in both women when the intra-amniotic infection was subclinical. High TNF-α serum concentrations have also been reported in patients with shock, which was not caused by demonstrable infection.[79]

There was no evidence of infection when the first patient was admitted in early labor while her TNF-α concentration was 1 ng/mL. Even the clinical manifestations of fever that developed 12 hours later (temperature elevations to 38.7°C and 39.2°C following an epidural in association with a normal WBC count) were tenuous at best. Yet, remarkably enough, this patient already carried a marker for the lethal catastrophe that was to befall her 14 hours later.

The second patient had a TNF-α concentration of 10 ng/mL, 100 times higher than the previously considered lethal concentration;[9] yet, the only clinical evidence of infection was premature labor refractory to tocolysis.[80] This patient was suspected to have infection because of the combination of preterm labor and foul-smelling amniotic fluid.

TNF-α concentrations in this high lethal range have been described without shock in patients with leprosy and Ethiopian cutaneous leishmaniasis, which are intracellular infections characterized by a massive pathogenic load.[81] It has been suggested that patients who

tolerate such high doses of TNF-α have circulating inhibitors of TNF-α that neutralize its biological activity.[82] Without such inhibitors, TNF-α induces severe side effects in patients, including hypotension. For example, in patients with cancer given TNF-α infusions to treat their malignancies, the maximal dose of TNF-α tolerated is limited by side effects and associated with undetectable serum TNF-α concentrations.[83]

Several studies reported the maternal circulating TNF-α concentrations during normal pregnancy.[84–97] In a recent study,[93] comparing 57 pregnant Finnish women throughout gestation and 62 control women matched for age and smoking, there were no differences in the median TNF-α concentrations in non-pregnant and pregnant women. Furthermore, the median TNF-α concentration in maternal serum did not differ significantly among the three trimesters, with a median (min-max) concentration of 2.28 $pg/mL^{-1}$ (1.28–5.4) during the third trimester. Similar findings with a lack of change in TNF-α concentration during pregnancy compared to the non-pregnant state[88;96] and with advancing gestational age[85;89] were reported by other investigators.

A few studies have addressed the question whether TNF-α concentration in maternal circulation changes during normal labor at term.[84;85;87;90] Consistently, these studies reported no change in TNF-α concentration in term labor.[84;85] Conflicting results, however, exist regarding changes in the context of preterm labor,[84;88;90] with only one study reporting significantly higher median concentration of TNF-α in patients with preterm labor than in controls.

Importantly, among all of these studies, the highest TNF-α concentration reported was in the range of 200–300 pg/ml.[88;95] In none of these studies did the concentration reach the range of 1 ng/mL.

## Amniotic fluid embolism or septic shock?

AFE was the clinical diagnosis in the first patient and part of the differential diagnosis in the second patient. The hemodynamic parameters first recorded after the onset of cardiopulmonary collapse in these patients (Table 1) were similar to those previously reported in patients with AFE.[1;9–20] We cannot discount the possibility that both patients had two pathological processes, one that caused their cardiopulmonary collapse (AFE) and another totally unconnected with it (sepsis). Autopsies were not performed at the request of the families.

Review of previously published case reports in which clinical findings were reported revealed that less than 10% of women in whom AFE was confirmed by autopsy had fever during labor or the puerperium prior to the onset of symptoms.[6;7;98–119] These patients invariably had prolonged rupture of the membranes or prolonged labor, suggesting that the infections were secondary and not present at the onset of labor. Moreover, in our patients TNF-α was elevated many hours before the onset of cardio-respiratory symptoms and DIC. For these changes to have been caused by AFE, embolization would have to have preceded the onset of symptoms by hours; however, this has never been observed in animal models of AFE.[6;28;98;120;121]

These findings have potentially far-reaching diagnostic and management[70;71;73;122;123] implications. First, by measuring plasma TNF-α and perhaps other cytokines/chemokines/inflammatory mediators, it may be possible to identify those patients at risk for developing septic shock. Alternatively, these determinations may serve to identify women who will have a hemodynamic decompensation among those with clinical chorioamnionitis. However, the relationship between plasma TNF-α concentrations (and other cytokines) and septic shock is complex. It is important to note that TNF-α can also induce tachyphylaxis.

The observations reported herein are important because many cases of maternal death that have been attributed to AFE may in fact have been caused by subclinical infections.[2;26;124–126] This is particularly likely with maternal deaths following first or second trimester abortions that have been attributed to AFE.[127;128] These cases have been particularly puzzling because the volume of amniotic fluid in the midtrimester is small and contains little particulate matter. These cases have been poorly documented and based on death certificates or unverified autopsy diagnoses. These are frequently inaccurate because medical records often retain the original diagnoses even when these are not confirmed by autopsy, and also because the histological material in the lungs may be misinterpreted.[26;129] The recognition that subclinical infections of the amniotic fluid cavity may cause a clinical picture indistinguishable from AFE should lead to earlier diagnosis and treatment of sepsis in these cases, and perhaps an improved outcome.

It is also possible that TNF-α and other inflammatory mediators produced in response to TNF-α may mediate the host responses to AFE, namely, cardiorespiratory failure, myocardial depression, pulmonary edema, and DIC, which are similar to the pathophysiological changes they mediate in septic shock. TNF-α is produced by monocytes and macrophages. Keratin elicits a foreign body giant cell reaction in the body as is frequently observed in ruptured epidermal inclusion cysts, well-differentiated squamous cell carcinomas and pilonidal sinuses.[130] Keratin is present in the fetal squames that embolize to the lung in AFE. Mucin, which is the component of amniotic fluid debris most commonly identified in the lungs,[114] can elicit a histiocytic tissue reaction as in ruptured mucinous cysts of the lip. Meigs[115] reported extensive macrophage mobilization and an intense phagocytic repose in the lungs of a patient who died of AFE, which caused sudden cardiopulmonary arrest in labor. The author postulated that the intense phagocytic response was to the granular material present in amniotic fluid debris.[115] Less dramatic macrophage responses have been reported by others.[103] Meigs[115] suggested that the intensity of the phagocytic response observed in histologic material will depend on the duration of symptoms prior to death because after some time the phagocytes dissipate and migrate to the lymph glands. Further research into this question is warranted.

## Meconium in the amniotic fluid, AFE and intra-amniotic infection

Meconium was present in the amniotic fluid of the first patient. This is noteworthy because experimental studies in animals indicate that amniotic fluid containing meconium is more likely to elicit the AFE syndrome than filtered amniotic fluid.[30;31;131] The traditional interpretation of this is that the particulate matter is responsible for the emboli in the maternal lung. However, we have previously reported that intra-amniotic infection is more common in patients with meconium-stained amniotic fluid, and we have also demonstrated that endotoxin can be detected more frequently in meconium-stained than in clear amniotic fluid.[132]

## Why did women develop cardiovascular collapse and DIC in the postpartum period?

Cardiovascular collapse and DIC may occur any time during the course of infection; yet, in our cases, it occurred in the immediate postpartum period. We have previously reported that trophoblast can deactivate neutrophils and monocytes upon contact.[133] Thus, maternal activated neutrophils and monocytes entering the intervillous space can change their biological properties (including the production of reactive oxygen radicals, NADPH oscillations and calcium spikes) after touching the villous trophoblast. Thus, pregnant women carry an “inactivation chamber” for cells of the innate limb of the immune response. We have proposed that this unique immune adaptation evolved to prevent rejection/damage of the placenta, which is 50% foreign. Contact deactivation of neutrophils and monocytes is however transient, because studies of flow cytometry have demonstrated that the phenotype

and metabolic properties of circulating cells is consistent with that of activation. We envision that upon delivery of the placenta, this "inactivation chamber" (the intervillous space of the placenta) is no longer available, and therefore, activated monocytes and neutrophils (because of infection) may lead to septic shock. Further studies are required to determine if most cases of septic shock associated with intra-amniotic infection occur in the postpartum period. We have recently determined the molecular basis for contact deactivation[133] and this may open avenues for the treatment of septic shock.

In conclusion, shock, presenting suddenly with cardiopulmonary collapse during labor, delivery or shortly after delivery, has been recognized as a distinct syndrome for many years, and usually is attributed to AFE.[1;2;6;98;134] We describe two cases in which postpartum shock and DIC occurring was associated with intraamniotic infection. These observations have implications for understanding the spectrum of disease of intrauterine infection during pregnancy and to develop means to identify the patient at risk for cardiovascular collapse and DIC. It is possible that early diagnosis and novel treatments help improve the prognosis of the patient at risk.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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