Clostridium perfringens Sepsis and Fetal Demise after Genetic Amniocentesis

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ABSTRACT

Clostridium perfringens is a rare cause of intrauterine infection. There have been five case reports concerning infection associated with invasive procedures. We report a woman who underwent a genetic amniocentesis due to her history of chronic granulomatous disease. She presented to the hospital ~38 hours after the amniocentesis complaining of fever and chills. Due to acute decompensation, she underwent an emergent dilatation and evacuation. During her stay, blood cultures came back positive for *C. perfringens*. Gradual improvement with intensive monitoring led to hospital discharge 4 days after the procedure. Uterine infection due to *C. perfringens* leading to maternal sepsis is associated with a high morbidity and mortality rate. Our patient was able to survive without a hysterectomy due to the rapid administration of antibiotics and surgical intervention while being evaluated.

KEYWORDS: *Clostridium perfringens*, *Clostridium welchii*, amniocentesis, sepsis, septic abortion

Clostridium perfringens, formerly known as *Clostridium welchii*, is a rare cause of intrauterine infection. Most reported cases of intrauterine *Clostridium* infection resulted from septic abortion,[1] with a reported incidence between 0.5 and 1.0%.[2] There have been three published case reports concerning *C. perfringens* infection associated with amniocentesis,[3–5] and two associated with cordocentesis.

CASE REPORT

A 23-year-old gravida 3, para 1011 at $17^{6}/_{7}$ weeks presented for an amniocentesis to determine whether her fetus was affected by chronic granulomatous disease, an X-linked disorder she had never been diagnosed with but had transmitted to her 9-month-old son. Past medical history was significant for depression, smoking 10 cigarettes per day, occasional marijuana use, and alcohol exposure in the beginning of the pregnancy. She also had asthma and was diagnosed by her primary care physician with a recent bout of bronchitis. The patient was treated with a 5-day course of low-dose oral corticosteroid that she had finished 1 week prior to presentation but no antibiotics. Past obstetric history was significant for a full-term vaginal delivery and a therapeutic termination. The remainder of her history is noncontributory. She used a fluticasone and salmeterol inhaler twice daily and an albuterol inhaler as needed.

Prior to the amniocentesis, fetal gender could not be confirmed with ultrasound. The genetic amniocentesis was performed under sterile conditions and without difficulty on a Friday at 11 A.M. A 22-gauge needle was

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passed into the right lower quadrant of her uterus, and 30 mL of clear fluid was extracted with the first attempt. The fetal heart rate after the procedure was within normal limits.

The patient presented to labor and delivery ~38 hours after the procedure complaining of fever of up to 102°F at home and subjective chills that started ~19 hours postprocedure. She had taken acetaminophen 3 hours prior to presentation. She also complained of decreased fetal movement, vaginal spotting, and leakage of foul-smelling fluid from her vagina.

Her vital signs on admission were temperature 99.7°F, pulse 97, respiratory rate 24, and blood pressure 125/79. She was noted to be anxious, shaking, and in painful distress. Her cardiopulmonary exam was significant for diffuse wheezing bilaterally with good air movement. Her abdomen was soft, but exquisitely tender over the uterine fundus. Sterile speculum exam revealed gross pooling of foul-smelling, purulent material, which was thought to be pus although the patient was suspected to have spontaneously ruptured her membranes earlier. The patient's cervix was long, thick, and closed on sterile vaginal exam.

A repeat temperature was noted to be 103.8°F and the patient was diagnosed with an inevitable septic abortion and asthma exacerbation. She received her first dose of piperacillin 3.375 g intravenously (IV) within 1 hour of arrival to labor and delivery and was additionally treated with IV hydration and a levalbuterol nebulizer. A complete blood count with differential, complete metabolic panel, and blood cultures were sent. A transabdominal ultrasound revealed a subjectively decreased amount of amniotic fluid and absence of fetal heart motion.

The patient was noted to be acutely decompensating, requiring 7 L of IV crystalloid fluid to maintain an adequate blood pressure. Given her current clinical condition, the decision was made to proceed to the operating room for an emergent dilation and evacuation. Her white blood cell count was noted to be 34.1 cells/mL with hemoglobin and hematocrit of 12.9 g/dL and 36.3%, respectively. She also had an elevated prothrombin time of 17.5 seconds with an abnormal international normalized ratio of 1.46. Her fibrinogen and partial thromboplastin time were normal. Misoprostol (50 μg) was placed rectally to aid with cervical dilation.

She was taken to the operating room and placed under general anesthesia. A large amount of foul-smelling purulent fluid spontaneously expelled from the uterus along with copious quantities of gas per the vagina. When the patient was placed in the dorsal lithotomy position, she spontaneously delivered an intact, macerated-appearing fetus. The placenta was evacuated using suction and sharp curettage under ultrasound guidance. Continued bleeding was noted from the uterus and 800 μg of misoprostol was placed in her rectum. The uterus was noted to retain tone and contracted appropriately. An ultrasound revealed no remaining products of conception in the uterus. It was also noted that though the patient had expelled gas per vagina prior to the procedure, no gas bubbles had been seen in the myometrium on ultrasound.

The blood loss was estimated to be 1000 mL, and the patient received an additional 2700 mL of crystalloid solution in the operating room. Whether her hypotension was from sepsis or symptomatic anemia due to the excessive blood loss, the patient required further blood pressure support with IV phenylephrine during and after the procedure, and she was transferred to the surgical intensive care unit (ICU) for further stabilization and treatment after the procedure. She remained in the ICU overnight while receiving IV pressors and fluids. Colloid infusion and blood transfusion were considered in the postoperative period; however, the patient's hematocrit remained stable around 22%. Piperacillin was continued every 6 hours for the remainder of her hospital course.

The patient showed gradual improvement, and in the interim her blood cultures revealed *C. perfringens* in one of the tubes. She was discharged home on hospital day 4 with a plan to continue amoxicillin clavulanate for 14 days per the recommendation of infectious disease specialists. Upon discharge, the patient's white blood cell count was noted to be $8.9 \times 10^3/\mu L$ with hemoglobin and hematocrit of 7.2 g/dL and 21.2%, respectively.

DISCUSSION

C. perfringens (formerly known as *C. welchii*) is a gram-positive, rod-shaped, anaerobic, spore-forming bacterium of the genus *Clostridium*. *C. perfringens* is ubiquitous in nature and can be found as a normal component of decaying vegetation, marine sediment, the intestinal tract of humans and other vertebrates, insects, and soil. It has also been isolated in 4% of prehysterectomy cervical cultures.[6]

Infections due to *C. perfringens* show evidence of tissue necrosis, bacteremia, emphysematous cholecystitis, and gas gangrene, which is also known as *clostridial myonecrosis*. The involved skin is initially pale and edematous and will progress to a bronze or magenta color, followed by a blue-black color with the formation of bullae. The bullae contain a clear or hemorrhagic discharge, sometimes with a "foul-sweet" odor. Pain and tenderness to palpation are usually disproportionate to the wound's appearance. In the case of uterine gas gangrene, onset is usually sudden with symptoms and signs consisting of fever, tachycardia, hypotension, renal failure, and jaundice. Radiography or other imaging may demonstrate gas in the uterine wall. Crepitus may be demonstrated on physical examination but may also be masked by significant edema. The urine often has a "port wine" color due to hemoglobinuria.

Although over 20 exotoxins are produced by *C. perfringens*, the main toxin involved in gas gangrene is known as α-*toxin* (lecithinase C), which inserts into the plasma membrane of cells, producing gaps in the membrane that disrupt normal cellular function. This toxin is responsible for rapid intravascular hemolysis with resultant dramatic anemia and jaundice in ~15% of patients who have bacteremia. Circulatory collapse can also occur due to the a-toxin suppression of cardiac contractility; this hypotension typically does not respond to fluid challenge.

The diagnosis of gas gangrene is usually based on the constellation of characteristic clinical features described previously, which can include myonecrosis, shock, and renal failure in the late stages. The differential diagnosis should include gas forming cellulitis, streptococcal myonecrosis, and necrotizing fasciitis. Early recognition is important because early institution of treatment has been shown to strongly influence the prognosis. The most important facet of treatment is prompt surgical debridement.

Gorbach et al[7] and Ohm and Galask[6] studied the cervical microflora of healthy women and reported *Clostridium* species present in 10 to 17% of cases. *C. perfringens* has been reported in 3 to 10% of healthy women as part of the normal vaginal flora.[4,7] However, only ~5% of the strains of *C. perfringens* are pathologically virulent.[2] The incubation period is usually several days but can be as short as 6 hours.[4]

As theorized in other case reports, this infection could have originated from insertion of the needle through maternal bowel during the amniocentesis. However, because the amniocentesis was done during direct visualization and no maternal bowel was noted in the path of the needle, this seems very unlikely. A recent case report describes a patient with a retroflexed uterus who underwent genetic amniocentesis and had multiple microbial organisms grow from a second amniocentesis due to the suspicion of chorioamnionitis. Bowel puncture was suspected to have inadvertently occurred during the first procedure due to the uterine position.[8] A pinhole in the sigmoid colon was demonstrated at laparotomy in one patient who had adhesions of bowel to the uterus.[9] Other postulated mechanisms that have not been proven include skin contamination of the patient or provider, preexisting subclinical chorioamnionitis, and ascending vaginal infection.

Postabortal sepsis due to *C. perfringens* is associated with a high mortality rate of 70% or more.[2] Approximately half of the reported cases occurred before the advent of antibiotics. However, even with the use of antibiotics, the outcome for these infections is poor.[2] The overall mortality rate is higher when infection induces intense hemolysis.[1] Hemolysis has been considered as the most significant and unfavorable prognostic sign associated with infection.

C. perfringens grows in necrotic tissues with an anaerobic environment. This underlines the importance of surgical removal of necrotic tissue that the microorganism requires to survive. Decker and Hall[2] suggested that curettage of the endometrial cavity could leave behind necrotic tissue and might possibly even traumatize healthy tissue, creating more necrotic tissue. The authors argued that *Clostridium* infection associated with sepsis was an indication for hysterectomy. Other authors have suggested that *Clostridium* infection associated with hemolysis is also an indication for hysterectomy.[10]

Three cases of *C. perfringens* infection following amniocentesis have been reported in the literature.[3–5] Fray et al[3] reported a case of amniocentesis under ultrasound guidance at 16 weeks' gestation. The patient was admitted 12 hours later and aborted an infected and macerated fetus. This patient received broad-spectrum antibiotics and underwent evacuation of her uterus. She later developed renal failure, *disseminated intravascular coagulation* (DIC), acute respiratory distress syndrome (ARDS), hemolytic anemia, and gram-positive septicemia. A total abdominal hysterectomy and bilateral salpingectomy was performed 6 hours after admission because of continuing hemolysis and severe hypotension. The patient gradually improved but required hemodialysis for 4 weeks.

Hovav et al[4] reported a case of amniocentesis under ultrasound guidance at 17 weeks' gestation. The patient presented 24 hours later with pyrexia and lower abdominal pain. Ultrasound showed a necrotic fetus with gas bubbles in the uterus. The patient developed DIC, ARDS, and acute renal failure. She received broad-spectrum antibiotics and underwent evacuation of the uterine cavity. A gradual recovery followed; the patient conceived 6 months later, and had an uneventful pregnancy and delivery.

Hamoda and Chamberlain[5] reported an amniocentesis done under ultrasound guidance at 16 weeks' gestation. The patient presented the following day with a fetal demise and gas pattern suggestive of *Clostridium* uterine infection on abdominal X-ray. The patient was placed on broad-spectrum antibiotics and underwent evacuation of the retained pregnancy products. The patient later developed DIC, ARDS, and acute renal failure. She recovered over a period of 2½ weeks and had a subsequent uneventful pregnancy. She had to undergo an emergent cesarean at term and was noted to have a uterine rupture from a 10-cm anterior fundal defect.

The outcomes of the more recent cases in addition to ours suggest that aggressive management with conservation of the uterus and ovaries may be a safe and effective option in the management of severe *Clostridium* infections. Aggressive management using antibiotics, endometrial curettage, and multidisciplinary team input may allow these rare but extremely ill patients the opportunity to achieve a subsequent pregnancy in the future.

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