Haemophilus influenzae Intra-Amniotic Infection With Intact Membranes

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Background: **Amnionitis rarely occurs with intact membranes. *Haemophilus influenzae* is a rare pathogen in intra-amniotic infection, but its importance and prevalence could be increasing, as reflected by the growing number of reported cases in the last 20 years.**

Methods: **Using the key words "amnionitis," "intra-amniotic infection," "chorioamnionitis," and "*Haemophilus influenzae*," we searched MEDLINE files from 1980 to the present. Articles dating before 1980 were accessed from cross-reference of the more recent studies.**

Results and Conclusions: H. influenzae, **a nonmotile, aerobic, gram-negative rod-shaped bacteria, is primarily responsible for respiratory tract infections in children and neonatal meningitis; it has a low prevalence rate in genital tract cultures but a high attack rate of infection in mothers and neonates. With intact membranes, intra-amniotic infection occurs rarely and is thought to be caused by hematogenous transplacental seeding, direct invasion of the fetal membranes, or inoculation of the amniotic fluid during an invasive procedure. It can also be idiopathic.**

It occurs most often in the second and early third trimesters and can be definitively diagnosed by a positive amniotic fluid culture or positive maternal or neonatal blood cultures and clinical evidence of intra-amniotic infection. We present a case of intra-amniotic infection with intact membranes at 15 to 16 weeks in a patient with clinical evidence of intra-amniotic infection and positive blood cultures whose infection was treated successfully with antibiotics, prolonging her pregnancy by 16 weeks.

Physicians caring for obstetric patients must be vigilant in diagnosing intra-amniotic infection, even with intact membranes, and this infection should be considered in the differential diagnoses for acute abdomen in pregnancy. (J Am Board Fam Pract 1994; 7:335-42.)

Intra-amniotic infection occurs in 1 to 4 percent of pregnancies and can lead to serious maternal and neonatal morbidity and, occasionally, death. It is typically an acute infection associated with ruptured membranes, maternal fever, and other specific findings (Table 1). Evidence of other causes for fever is absent. Intra-amniotic infection, or clinical amnionitis, must be distinguished from chorioamnionitis, which is often a histologic diagnosis without clinical correlation. Intra-amniotic infection is commonly a mixed aerobic-anaerobic polymicrobial infection. Delivery is usually part of the management plan for treating an intra-amniotic infection.

Methods

We report a case of *Haemophilus influenzae* intra-amniotic infection with intact membranes that was successfully treated with antibiotics without delivery. Using the key words "amnionitis," "intra-amniotic infection," "chorioamnionitis," and "*H. influenzae*," MEDLINE files were searched through the CD ROM system from 1980 to the present. Articles dating before 1980 were accessed from cross-reference of the more recent studies.

Case Report

A 21-year-old woman, gravida 3, para 2, at 15 weeks' gestation by dates and second-trimester sonogram, was brought to the emergency department by ambulance complaining of fever, chills, anorexia, vomiting, vaginal bleeding, and crampy, lower abdominal pain.

Four days earlier she had reported drainage of a clear fluid, a whitish vaginal discharge, and left lower quadrant pain. When she was examined at that time, her blood pressure and pulse rates were normal with no orthostatic change, and she was afebrile. She was noted to have left lower quadrant tenderness with rebound. Dried blood was found in the vaginal canal, but she had a closed

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Table 1. Diagnostic Criteria for Intra-amniotic Infection.*

Maternal fever (≥37.8 °C or 100 °F)
Absence of other localized source of infection
Two or more of the following:
Maternal tachycardia (pulse >100 beats per minute)
Fetal tachycardia (pulse >160 beats per minute)
Uterine tenderness
Foul odor or amniotic fluid
Maternal leukocytosis (white cell count >12,000/mm³)

*From Gibbs, et al.

cervical os. There was no objective evidence of ruptured membranes. The adnexae were tender bilaterally, and her uterus was appropriately sized. Fetal heart beat was not detected in the office. A subsequent sonogram showed a viable 15.1-week fetus and a small (1 cm) subchorionic hemorrhage in the lower uterine segment. The placenta was posteriorly located and normal. Amniotic fluid volume was normal. With reassuring findings on the sonogram and an absence of fever, she was cared for expectantly. She continued to have occasional episodes of vaginal spotting.

Two days before admission, at a scheduled follow-up visit, she reported more severe cramping. Her blood pressure was 110/70 mmHg with a pulse rate of 100 beats per minute, and she was afebrile. No active bleeding was seen from the cervix, and the fetal heart rate was 140 beats per minute. Threatened abortion remained a tentative diagnosis, and rest was advised. The next day she reported a temperature of 102°F, chills, and a small amount of vomiting but did not seek medical attention.

When she arrived at the emergency department, she reported vomiting once in the morning and drinking nothing all day. Her abdominal pain and vaginal bleeding had increased acutely about 3 hours before arrival in the emergency department. She had noted a yellow-to-clear vaginal discharge for 2 days. During her examination, she appeared uncomfortable but was alert. Her blood pressure was 109/71 mmHg, and her pulse rate was 106 beats per minute. Asymptomatic orthostatic change was noted. Her temperature was 101.4°F with shaking chills. Her abdomen was soft, and she had moderate low abdominal-uterine tenderness with mild rebound but no guarding. Her bowel sounds were normoactive. On a speculum examination a moderate amount of red blood was seen oozing from the cervical os. There was a marked ectropion, but there were no clots, fetal tissue, or discharge in the vagina. On a bimanual examination, the cervical os was closed. Her cervix, however, was markedly tender, as were the uterus and adnexae (left side more tender than the right side).

A repeat sonogram showed a viable fetus. The subchorionic hemorrhage had increased in size to $2.2 \times 1.3 \times 1.6$ cm, and her adnexae looked normal. The amniotic fluid volume was normal. Laboratory data showed a white cell count of 14,000/mm³ with 67 percent segmented neutrophils, 22 percent band cells, 8 percent lymphocytes, and 3 percent monocytes. Hemoglobin was 11.6 g/dL, platelets were 194,000/mm³, and blood type was O negative. Liver function tests were normal. Urinalysis was normal, except for ketonuria (80 mg/dL).

Her medical history was noteworthy. During this pregnancy, she had had several hours of painless vaginal bleeding on three occasions (at 9, 12, and 13 weeks' gestation). The last episode of bleeding had been associated with leakage of clear fluid from her vagina; however, because she had not been examined by a physician, we did not know whether this fluid was consistent with amniotic fluid. Her previous pregnancies had been uncomplicated. She had had chlamydial cervicitis and trichomoniasis 3.5 years earlier. She currently had 1 sexual partner. She had temporarily discontinued oral contraceptive pill use a few weeks before conception because of financial concerns and was using condoms irregularly. She was a smoker. She took no medications.

She was admitted to the hospital with diagnoses of pregnancy, subchorionic hemorrhage, and intra-abdominal versus intra-amniotic infection. She received Rh_0 immune globulin and aggressive intravenous hydration. Antibiotic therapy was begun with ampicillin, clindamycin, and gentamicin after cultures of cervix, urine, and blood were obtained. Ampicillin was subsequently changed to cefoxitin after one dose, when the patient reported an earlier episode of hives with penicillin, despite the 3 to 7 percent likelihood of cross-allergy to cephalosporins.

Her condition progressively declined. Fourteen hours after presentation, abdominal pain had worsened, and she had five episodes of diarrhea. On examination, she had marked rebound tenderness, and a surgeon was consulted. The con-

sultant surgeon found her abdomen to be rigid with marked lower abdominal tenderness to light percussion and agreed with the diagnosis of acute peritonitis with a differential diagnosis of septic abortion, acute pelvic inflammatory disease, ruptured left tubo-ovarian abscess, or ruptured appendicitis. The surgeon promptly performed an exploratory laparotomy and incidental appendectomy. Laparotomy revealed an essentially normal abdomen, except for a slight amount of cloudy peritoneal fluid, which was aspirated and cultured (negative). A Gram stain of the peritoneal fluid showed no white cells or microorganisms. Microscopic examination of the appendix showed mild, acute inflammation of the serosal surface, consistent with peritonitis.

Initial blood cultures were positive at 24 hours for gram-negative rod-shaped bacteria. Final cultures were positive for *H. influenzae* in three out of four bottles. *H. influenzae* was β-lactamase positive and therefore resistant to ampicillin, but it was sensitive to ceftriaxone and moderately sensitive to cefaclor. Cervical cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were negative. Vaginal culture for group B streptococcus was negative. Urine culture for pathogens was negative. Findings on sinus films and a chest radiograph were normal, and the patient had no symptoms referrable to these areas. Findings on a sonogram of the retroperitoneum were also normal.

About 12 hours postoperatively, the patient became febrile to 104.5°F, but she was clinically improved. A blood culture obtained at that time for *H. influenzae* was subsequently negative. Her symptoms rapidly improved, and by 48 hours postoperatively, she was afebrile, and her white cell count was 5900/mm^3 with a normal differential. After 5 days of intravenous antibiotics, she was prescribed cefaclor 500 mg by mouth every 6 hours for an additional 14 days. A repeat sonogram on the 4th postoperative day showed no evidence of subchorionic hemorrhage. She was discharged on the 5th postoperative day with prescriptions for cefaclor and iron supplements.

Approximately 16 weeks later, at 31-plus weeks' gestational age, she arrived at another institution with preterm labor and intact membranes. She subsequently had a spontaneous vaginal delivery of a double footling breech 3 lb 8.5 oz (1588 g, 50th percentile) female infant with 1- and 5-minute Apgars of 5 and 6. The mother's postpartum course was unremarkable, although her infant was hospitalized for 5.5 weeks for prematurity, respiratory distress syndrome (requiring intubation and mechanical ventilation for 4 hours), hyperbilirubinemia, and suspected sepsis (with negative cultures). This infant exhibited developmental delay on subsequent examination, with fine motor skills (Peabody Developmental Fine Motor Scale) of a 7-month-old at 11 months corrected age and of a 10-month-old at 15 months corrected age. She was also mildly hypotonic. As of 15 months corrected age, no additional medical problems were observed.

Discussion

H. influenzae is a nonmotile, aerobic, gram-negative rod-shaped bacteria. It is primarily responsible for respiratory tract infections in children and for neonatal meningitis. It has been implicated, however, in many other types of infection

Table 2. Types of *Haemophilus influenzae* Infections.*

Gynecologic
Bartholinitis
Endometritis
Pelvic inflammatory disease
Tubo-ovarian infections
Urinary tract infections
Vaginitis
Obstetric
Amnionitis or chorioamnionitis
Bacteremia (usually with benign course)
Endometritis
Premature rupture of membranes
Postparum fever
Spontaneous abortion and stillbirth
Neonatal
Conjunctivitis
Endocarditis
Meningitis
Pericarditis
Pneumonia
Sepsis
Pediatric-Adult
Arthritis
Bacteremia
Cellulitis
Conjunctivitis
COPD† exacerbation
Epiglottitis
Otitis media
Pneumonia
Sinusitis

*Adapted from Foldes and Eilam.[2]
†COPD=Chronic obstructive pulmonary disease.

(Table 2). Although neonatal, perinatal, and genital tract infections caused by *H. influenzae* strains were first reported in the early 1900s, a literature review located fewer than 50 cases of perinatal sepsis caused by *H. influenzae* from 1909 to 1981.[3] The number of reported cases has grown markedly in the last 20 years, reflecting either increased recognition or increased prevalence. For example, in a series of 21,034 births, perinatal infection caused by *H. influenzae* was reported in 0.64 of 1000 births from 1979 through 1984 and in 2.83 of 1000 births from 1985 through 1987.[4] Moreover, a recent 8-year study in Louisville, KY, found *H. influenzae* to be the third most common cause of early-onset neonatal sepsis (8 percent of cases), following group B streptococcus and *Staphylococcus epidermidis*.[5] Mortality associated with neonatal sepsis caused by *H. influenzae* is high.

Based on concordance of *H. influenzae* serotypes of maternal-infant pairs, positivity of neonatal blood cultures obtained shortly after birth, positivity of neonatal gastric aspirate (amniotic fluid) cultures, and other factors, it appears that most, if not all, cases of early-onset neonatal *H. influenzae* sepsis are due to vertical transmission from an amniotic fluid infection that could have begun before rupture of membranes. Most complicated genital tract infections originate from the commensal flora of the lower genital tract. Studies of *H. influenzae* isolates do not support the concept of specific genital strains.[4] Unlike group B streptococcus, *H. influenzae* appears to have a low prevalence rate (1 percent or less) in genital tract cultures but a high attack rate of infection in mothers and neonates (up to 50 percent).[6,7]

During the last 20 years, a relatively high incidence of β-lactamase-positive strains of *H. influenzae* has been noted in many locations. In a 1983 literature review of perinatal sepsis, Wallace, et al.[3] noted all *H. influenzae* isolates were uniformly sensitive to ampicillin. In contrast, a 1989 study of 84 *H. influenzae* strains from genitourinary or neonatal infections found that 8.3 percent of strains were β-lactamase positive and ampicillin-resistant; these 8.3 percent of strains were sensitive to a third-generation cephalosporin (cefotaxime).[4] Unfortunately, few of the cases reviewed for this report included antibiotic sensitivity testing of *H. influenzae* isolates. Of the three studies that did report such data, however, 21 of 23 *H. influenzae* isolates (from various maternal and neonatal sites) were sensitive to ampicillin. In contrast, most infectious disease experts consider approximately 25 percent of *H. influenzae* type b and nontypeable *H. influenzae* to be ampicillin-resistant. Such isolates are generally sensitive to second- and third-generation cephalosporins (e.g., cefaclor, cefotaxime, and ceftriaxone), amoxicillin-clavulanate, and sulfonamides.

Bacterial colonization and infection of the amniotic cavity have received considerable study recently, mostly in an effort to prevent preterm births.[8] Although bacterial colonization of amniotic fluid was once considered an indication for delivery, recent studies have found a 5.5 percent rate of positive amniotic fluid cultures in asymptomatic, afebrile women at 20 to 35 weeks[9] and a 10 percent rate of positive amniotic fluid cultures in afebrile women at term with intact membranes.[10] Some authors believe that bacterial colonization might lead to subclinical or clinical intra-amniotic infection, particularly with the onset of labor.[11] Intra-amniotic infection rarely occurs in women whose membranes are intact.[12] Nonetheless, depending on criteria used to define intra-amniotic infection (see discussion below), at least 16 cases of *H. influenzae*-positive intra-amniotic infection with intact membranes have been reported.[11,13-18]

Intra-amniotic infection is largely an ascending infection, especially after rupture of membranes.[19] At least three mechanisms have been proposed to explain the pathogenesis of intra-amniotic infection with intact membranes[12]: (1) hematogenous, transplacental seeding (by *Listeria monocytogenes* and group A streptococcus), (2) direct invasion of the fetal membranes (by group B streptococcus and *Escherichia coli*), and (3) inoculation of the amniotic fluid during an invasive procedure, such as amniocentesis, cordocentesis, or cerclage placement. Hematogenous, transplacental seeding might account for two cases of *H. influenzae*-positive intra-amniotic infection with a documented distant focus of infection (pneumonia, sinusitis) and subsequent bacteremia.[13,14] In contrast, other reported cases of *H. influenzae*-positive intra-amniotic infection with intact membranes appear to be idiopathic, without any obvious pathogenic mechanism.[11,15-18]

Intra-amniotic infection with intact membranes accounts for considerable perinatal morbidity and mortality,[20] including maternal and

neonatal bacteremia or sepsis, endometritis, increased rate of uterine atony, a two- to threefold increased incidence of Cesarean section, increased rate of dystocia, and complications associated with prematurity.[12,21] The rate of intra-amniotic infection with intact membranes peaks between 20 and 26 weeks and beyond 37 weeks.[20] This bimodal distribution has been attributed to the protective effect of an antimicrobial polypeptide that appears in amniotic fluid after 26 weeks.[22]

Diagnosis of intra-amniotic infection remains elusive, despite clinical criteria (Table 1). Earlier studies have used various maternal and neonatal culture sites to document intra-amniotic infection. Most authors would agree with a definitive diagnosis of intra-amniotic infection in the presence of a positive amniotic fluid culture (>100 colony-forming units per milliliter [CFU/mL] of one or more microorganisms) obtained by amniocentesis or needle aspiration of intact membranes at Cesarean section and clinical evidence of intra-amniotic infection. Cultures obtained from other sites or by other methods, however, are less reliable. Several studies have relied upon positive cultures of amniotic fluid obtained through an intrauterine pressure catheter (after discarding several initial cubic centimeters of amniotic fluid to decrease likelihood of cervicovaginal contamination)[23-25] or obtained by needle aspiration of intact membranes through a vaginal approach, following a povidone-iodine preparation.[11] Amniotic fluid cultures obtained by these methods, as well as cultures of the maternal genital tract (e.g., vagina, cervix, endometrium, and placenta), have been criticized as providing insufficient evidence of intrauterine infection because of possible contamination with infected blood in the cervix or vagina or because of cervicovaginal colonization.[26]

Placental cultures, even if obtained under sterile conditions at Cesarean section, do *not* correlate with cervical cultures or with neonatal cultures.[26,27] In contrast, a positive maternal or neonatal blood culture in the setting of clinical intra-amniotic infection is probably diagnostic. Nonetheless, a negative (bacterial) amniotic fluid culture does *not* exclude the diagnosis of intra-amniotic infection, as the infection could be limited to the membranes or placenta or could be caused by other microorganisms, such as viruses, mycoplasma, or chlamydia.[11] Cultures of neonatal surfaces, nasopharynx, and gastric aspirates — which, theoretically, should be bathed in amniotic fluid — are viewed as less reliable evidence of intra-amniotic infection, unless they correlate with a valid maternal culture (such as the same *H. influenzae* serotype). One study[18] did show that 70 percent of neonates with blood cultures positive for *H. influenzae* had a positive culture from at least one surface site, such as the surface of the ear.

Finally, histologic evidence of chorioamnionitis by itself is inadequate to diagnose clinically serious intra-amniotic infection. Histologic inflammation occurs much more commonly than does clinical intra-amniotic infection. In one study of 95 women with preterm delivery (less than 35 weeks), clinical intra-amniotic infection was diagnosed in 33 percent of patients with histologic evidence of chorioamnionitis and in 7 percent of those without such evidence.[29]

The case presented in this report appears to represent intra-amniotic infection caused by *H. influenzae* with subsequent maternal sepsis. Supportive evidence for this diagnosis includes maternal history, examinations, and clinical course, with many similarities to earlier case reports (see below); peritonitis by examination with normal findings on exploratory laparotomy; and positive maternal blood cultures for *H. influenzae*, with clinical evidence of sepsis, in the absence of physical, laboratory, or radiologic evidence of another source for this microorganism. In contrast, evidence against the diagnosis of intra-amniotic infection caused by *H. influenzae* could include rapid resolution of illness, presence of intact membranes, and continued gestation (for an additional 16 weeks). In retrospect, additional support for intra-amniotic infection could have been obtained through transabdominal amniocentesis or perhaps even a positive vaginal culture for *H. influenzae* of the same serotype as that obtained by blood culture. Nonetheless, we believe this patient did have intact membranes based on a physical examination and sonogram, even though two historical points raised the possibility of ruptured membranes.

Many features of this case are similar to those in other reported cases of *H. influenzae* intra-amniotic infection with intact membranes. Most reported cases occurred in the second trimester or early third trimester; our case occurred at 15 to 16 weeks. Complaints of change in vaginal discharge, vaginal bleeding, abdominal pain, fever,

and chills are extremely common in reported cases as well.[13,15,17,18,30] Sepsis with high fever and hypotension has been reported previously,[13,15] particularly in cases in which *H. influenzae* intra-amniotic infection was associated with rupture of membranes.[30,31] Peritonitis with rebound tenderness has been reported in *H. influenzae* intra-amniotic infection with intact[13] and ruptured[32] membranes. Maternal leukocytosis with left shift was universal in reported cases. Maternal blood cultures were positive for *H. influenzae* (most commonly, nontypeable isolates) in 4 of 13 cases (31 percent) in which they were obtained.[13-18] This incidence of bacteremia is considerably higher than that reported for all causes of intra-amniotic infection (up 10 percent),[33] perhaps reflecting the virulence of *H. influenzae*. Only two of these four positive blood cultures could be attributed to distant foci of infection (i.e., respiratory tract) with subsequent hematogenous, transplacental seeding.[13,14] Finally, of the 16 cases of *H. influenzae* intra-amniotic infection with intact membranes that we found in the literature, all women were delivered of their infants during the illness; at least three of the infants died or were stillborn.

There is, however, evidence of successful treatment of two cases of intra-amniotic infection with antibiotics but without immediate delivery. In both cases membranes were ruptured. Romero, et al.[34] reported a case of a woman at 29 weeks with premature rupture of membranes, whose condition was managed expectantly. Cultures obtained by amniocentesis on hospital day 6 grew *Bacteroides bivius* (50,000 CFU/mL), *Veillonella parvula* (50,000 CFU/mL), and *Peptococcus* (7000 CFU/mL), with negative blood cultures. After 7 days of intravenous ampicillin, gentamicin, and clindamycin, a repeat amniotic fluid culture was negative, and there was no clinical evidence of intra-amniotic infection. Three days later labor was induced because of abnormal antepartum testing (with mature lung indices). There were no postpartum or neonatal complications. This case clearly documents the ability to sterilize amniotic fluid via parenteral antimicrobial therapy. In a related case, Monif[35] reported that a woman with premature rupture of membranes at 22 weeks had her gestation prolonged 42 days with antimicrobial therapy for intra-amniotic infection and bacteremia attributed to group G β-hemolytic streptococcus. A viable infant was delivered at 27-plus weeks following recurrent intra-amniotic infection, with maternal blood cultures positive for *Escherichia coli* and *Klebsiella pneumoniae*. Unfortunately, no amniotic fluid cultures were obtained, so absolute bacteriologic proof of intra-amniotic infection is lacking. Nonetheless, this case does suggest that bacteriologic cure of maternal and fetal infection can be achieved even with rupture of membranes.

Summary

In summary, we believe our case demonstrates successful antimicrobial treatment of *H. influenzae* intra-amniotic infection with intact membranes and prolongation of pregnancy by 16 weeks. A combination of three antibiotics (e.g., a second- or third-generation cephalosporin, gentamicin, and clindamycin) appears to be appropriate empiric treatment for presumed intra-amniotic infection or other causes of peritonitis in pregnancy based on our case and others reported in the literature. Ampicillin is no longer appropriate empiric therapy for *H. influenzae*. Physicians caring for obstetric patients must be vigilant in diagnosing intra-amniotic infection, even with intact membranes. Intra-amniotic infection must also be considered in the differential diagnosis for acute abdomen in pregnancy.

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