



Intra-Amniotic *Candida* Infection Treated by Liposomal Amphotericin B in a Patient with Cervical Insufficiency

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Intra-amniotic *Candida* infection is uncommon but the consequence can be catastrophic. Transcervical amphotericin B and intra-amniotic fluconazole administration were identified in the literature. We present a case with intact membranes and ongoing pregnancy treated by maternal intravenous liposomal amphotericin B. A primipara who underwent cerclage placement before fetal viability was diagnosed with intra-amniotic *Candida* infection. Although maternal intravenous liposomal amphotericin B eradicated fungi in the amniotic cavity, *Escherichia coli* invasion caused devastating chorioamnionitis. The newborn delivered at 27⁺³ weeks' gestation did not survive due to respiratory distress syndrome and sepsis. Despite negative conversion of intra-amniotic culture results for fungi after treatment, another pathogen such as bacteria could ascend into the amniotic cavity via weakened membranes. Clinicians should consider broad-spectrum antibiotics as well as antifungal agents in this setting.

Key Words: Amniotic fluid, Infection, *Candida albicans*, Liposomal amphotericin B, Uterine cervical insufficiency

Introduction

Compared with frequent vaginal candidiasis in pregnancy, intra-amniotic *Candida* infection is relatively uncommon and occupied 2.2–6.5% among patients with positive amniotic fluid culture results and preterm labor or preterm premature rupture of membranes.¹ Some authors reported that intra-amniotic *Candida* infection was commonly associated with retained foreign body (e.g., intrauterine contraceptive device and cerclage placement) in the uterine or vaginal cavity.^{1,2} However, the consequence of it can be catastrophic. It has been reported to cause from skin diseases to mortalities or significant morbidities such as congenital pneumonia, respiratory distress syndrome, broncho-pulmonary dysplasia, sepsis, or cerebral candidiasis.¹

Because of this fatality and paucity of effective treatment modalities in pregnancy, a majority of experts and clinicians have recommended prompt delivery. Therefore, the diagnosis of intra-amniotic *Candida* infection during previable periods presents a therapeutic dilemma for attending physicians. Until now, there were only three cases reported by two authors which presented maternal or intra-amniotic antifungal agents therapy to ongoing pregnant women who were diagnosed with intra-amniotic *Candida* infection proved by transabdominal amniocentesis.^{3,4} We present the first case of intra-amniotic *Candida* infection which underwent emergent cervical cerclage due to cervical incompetence and was treated with maternal intravenous liposomal amphotericin B.

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Case

A 40-year-old woman, gravida 4, para 1, was referred at 21⁺⁰ weeks' gestation for management of cervical insufficiency. She conceived by *in vitro* fertilization. Her previous obstetric history included two spontaneous abortion and one uncomplicated cesarean delivery at term. Her previous medical history was unremarkable.

On physical examination, severely bulging fetal membranes abutting on vaginal wall and reaching vaginal introitus were seen. She was asymptomatic except for recently increased vaginal discharge. Ultrasonographic examination showed a live fetus with appropriate estimated fetal weight for gestational age and no definite structural abnormalities. Emergent cervical cerclage was performed successfully. Based on previous reported data,⁵ the patient underwent the first transabdominal amniocentesis on hospital day 1. Amniotic fluid (AF) was transported immediately to the laboratory for Gram staining and for determining total cell count and differential cell count. Then, it was cultured for aerobic and anaerobic bacteria and for genital Mycoplasmas (*Ureaplasma urealyticum* and *Mycoplasma hominis*). AF white blood cell (WBC) count was 0/ μ L. No organisms were seen on Gram stain. However, we started third generation cephalosporin, clarithromycin, and metronidazole as broad-spectrum antibiotics since hospital day 1 because it was concerned about ascending microbial invasion by exposure of fetal membranes to the vaginal microbial environment. Two days later, it was reported that *Candida albicans* was grown. The patient underwent the second trans-

abdominal amniocentesis on hospital day 4. AF WBC count increased to 950/ μ L and *Candida albicans* was also grown from the retrieved AF.

Because fetal infection caused by *Candida albicans* can be fatal and there was no established standard treatment during pregnancy,¹⁻⁴ the attending physician strongly recommended release of cerclage knot and termination of index pregnancy. However, the patient wanted to continue the pregnancy and refused cerclage removal. After obtaining informed consent and consultation to division of infectious diseases of internal medicine, broad-spectrum antibiotics were stopped and the patient was switched to maternal intravenous amphotericin B (500 mg once) on hospital day 4. On that day, she complained of severe injection site pain, intractable vomiting, and febrile sensation. On hospital day 5, therefore, it was started to administer maternal intravenous liposomal amphotericin B 200 mg daily and 500 mg clotrimazole vaginal suppositories weekly (Fig. 1). Serial amniocentesis was conducted at approximately weekly intervals. AF culture was negative since the third amniocentesis on hospital day 11 (Table 1). After two consecutive negative results in AF culture, liposomal amphotericin B was

Table 1. AF WBC Count and Culture Results

Serial amniocentesis	AF WBC count (/ μ L)	AF culture result
Hospital day 1	0	<i>Candida albicans</i>
Hospital day 4	950	<i>Candida albicans</i>
Hospital day 11	20	No growth
Hospital day 24	2	No growth

Abbreviations: AF, amniotic fluid; WBC, white blood cell.

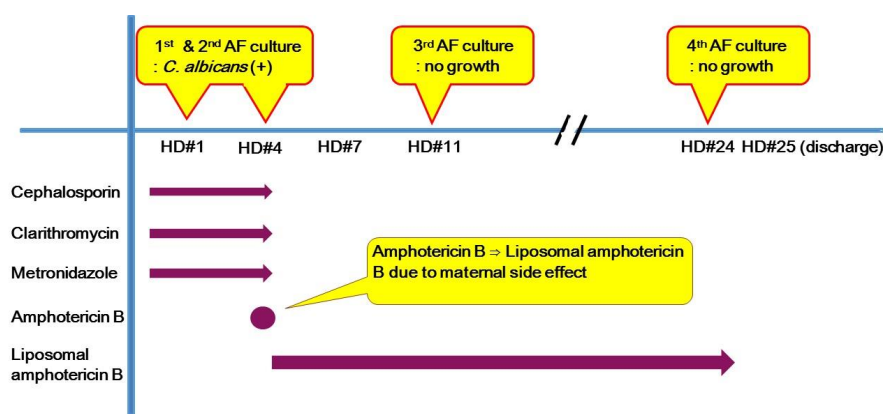


Fig. 1. Time table of use of broad-spectrum antibiotics and antifungal agents. AF, amniotic fluid; HD, hospital day.

stopped and the patient at 25⁺⁰ weeks' gestation was discharged on hospital day 25. After discharge, weekly follow-up at our outpatient's clinic was conducted.

During the follow-up periods, she was asymptomatic but had increased vaginal discharge and frequent loose stool three to four times a day. A sterile speculum examination revealed no signs of AF leakage from cervical os and absence of AF pooling in the posterior fornix. And the nitrazine test was negative. Toxin assay for *Clostridium difficile* was also negative. At 27⁺³ weeks' gestation, the patient was admitted with severe abdominal pain, fever of 38.4°C, vaginal bleeding, and rupture of membranes. Emergent cesarean delivery was performed, with a diagnosis of clinical chorioamnionitis and previous history of cesarean section. A 1,200 g-male infant was delivered but died 24 hours after birth due to severe respiratory distress syndrome and septic shock. Gross examination of the placenta showed no plaque-like lesions on the placental surface. Histopathological examinations of the placenta revealed severe acute chorioamnionitis and funisitis. Umbilical cord blood and skin culture at birth was positive for *Escherichia coli*. *Candida albicans* was not isolated from skin, throat, and blood of the newborn.

Discussion

Although vaginal colonization of *Candida* species occurs in approximately 25% of pregnancy, the incidence of ascending infection is very low.¹ Intra-amniotic *Candida* infection is frequently associated with retained intrauterine device or cerclage placement.^{1,2,4} In the case presented in this report, it is considered that protruding fetal membranes due to cervical insufficiency might be a predisposing factor for ascending intrauterine fungal infection.

According to reported data from conventional amphotericin B use during pregnancy, cord blood and placenta level of amphotericin B remained within the minimum inhibitory concentration ranges for up to 4 weeks after the last dose of the drug.⁶ Although the exact mode of elimination of amphotericin B remains to be clarified, the researchers suggested that the agent accumulates in tissues that then acts as a reservoir from which amphotericin B is slowly released back into circulation.⁶

Considering stages of ascending intra-amniotic infection,⁷ the need for additional intra-amniotic antifungal agents or transcervical drug transfer and the optimal treatment of these patients remain in question. The present case showed a clinical possibility to eradicate intra-amniotic fungi by maternal intravenous liposomal amphotericin B without additional intra-amniotic or transcervical administration of antifungal agents. The last dose of liposomal amphotericin B was administered at 24⁺⁶ weeks' gestation. Although *E. coli* sepsis was evident at delivery, the newborn at 27⁺³ weeks' gestation had no evidence of fungal infection based on culture studies from umbilical cord blood, skin, and throat secretion at least 18 days after the last dose of liposomal amphotericin B.

Systemic polyenes including conventional and liposomal amphotericin B are recommended as the first-line treatment regimen for invasive fungal infection during pregnancy because it is regarded as the safest systemic antifungal drug in pregnancy.⁸ Amphotericin B or liposomal amphotericin B are classified as category B by the Food & Drug Administration (FDA). On the contrary, the FDA reclassified fluconazole from category C to category D except for single-dose use for vaginal candidiasis.⁹ Although it is relevant to higher dose and longer duration therapy in the early first trimester, it is considered that use of oral azole antifungal agents should be limited to cases of maternal life-threatening infection.

Another point is that the newborn died from *E. coli* sepsis despite eradication of intra-amniotic fungi. The patient had complained of loose stool several times about a week before delivery. This might result in vaginal contamination by feces and enabling colonic bacteria to ascend into amniotic cavity via weakened fetal membranes.

In conclusion, single therapy of maternal intravenous liposomal amphotericin B is safe and effective to eliminate *Candida albicans* in the amniotic cavity. Despite negative conversion of intra-amniotic culture results for fungi during antifungal agents therapy, another pathogens such as bacteria could ascend into the amniotic cavity via weakened fetal membranes. Therefore, clinicians should consider broad-spectrum antibiotics as well as antifungal agents in treatment of intra-amniotic *Candida* infection.

References

- 1) Chaim W, Mazor M, Wiznitzer A. The prevalence and clinical significance of intraamniotic infection with candida species in women with preterm labor. Arch Gynecol Obstet 1992;251:9-15.
- 2) Roqué H, Abdelhak Y, Young BK. Intra amniotic candidiasis. Case report and meta-analysis of 54 cases. J Perinat Med 1999;27:253-62.
- 3) Shalev E, Battino S, Romano S, Blondhaim O, Ben-Ami M. Intraamniotic infection with candida albicans successfully treated with transcervical amniocentesis of amphotericin. Am J Obstet Gynecol 1994;170(5 Pt 1):1271-2.
- 4) Bean LM, Jackson JR, Dobak WJ, Beiswenger TR, Thorp JA. Intra-amniotic fluconazole therapy for candida albicans intra-amniotic infection. Obstet Gynecol 2013;121(2 Pt 2 Suppl 1):452-4.
- 5) Lee SE, Romero R, Park CW, Jun JK, Yoon BH. The frequency and significance of intraamniotic inflammation in patients with cervical insufficiency. Am J Obstet Gynecol 2008;198:633.e1-8.
- 6) Dean JL, Wolf JE, Ranzini AC, Laughlin MA. Use of amphotericin B during pregnancy: case report and review. Clin Infect Dis 1994;18:364-8.
- 7) Kim CJ, Romero R, Chaemsathong P, Chaiyasit N, Yoon BH, Kim YM. Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance. Am J Obstet Gynecol 2015;213(4 Suppl):S29-52.
- 8) Pilmsis B, Jullien V, Sobel J, Lecuit M, Lortholary O, Charlier C. Antifungal drugs during pregnancy: an updated review. J Antimicrob Chemother 2015;70:14-22.
- 9) Vlachadis N, Iliodromiti Z, Vrachnis N. Oral fluconazole during pregnancy and risk of birth defects. N Engl J Med 2013;369:2061-2.