

Coccidioidomycosis during pregnancy

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Background

Hi Heather,

I have a been talking to a St. Louis ID physician who is caring for an African-American female physician who has cutaneous cocci. First developed during her first pregnancy, reactivated when she had a second pregnancy not receiving antifungals, and now, after a year of itraconazole, wants to become pregnant again. At this point her cocci is very well controlled and there are no active lesion. She understands the issues and is willing to start amphotericin B during the first trimester with the intent of switching to oral azoles for the rest of the pregnancy. The question is whether she should begin amphotericin B prior to conception or, based on embryology, would it be equally safe to wait until a pregnancy test first became positive. Any thoughts?...

John

Statement of the problems

- Coccidioidomycosis is more severe when acquired during pregnancy
- Use of azole antifungals during pregnancy can be teratogenic

History

- In 1941, Farness reported the first case of severe coccidioidomycosis resulting in death in a pregnant woman in Tucson
- Vaughn & Ramirez (1951) observed that the risk of severe coccidioidomycosis increased with trimester
 - Among 28 cases in Kern County, CA
 - all 5 who developed disease prior to pregnancy did well
 - 1 of 12 women died with coccidioidomycosis during the 1st trimester
 - 1 developed meningitis and 1 died among 5 in the 2nd trimester
 - 7 of 11 died during the 3rd trimester
 - In all cases, the newborns did well

More recent descriptions

- Recent surveys have suggested that the prevalence of severe coccidioidomycosis during pregnancy has decreased
- Wack et al (1988) identified only 10 cases among 47,120 pregnancies in Tucson
 - all 7 in the 1st & 2nd trimester did well
 - 3 were diagnosed post-partum
 - 2 developed disseminated disease
- Caldwell et al (2000) reported on 32 cases occurring during the 1993 epidemic in California
 - 3 cases disseminated
 - no fetal deaths

Clinical severity of coccidioidomycosis increases the later it is acquired during pregnancy

	Infection acquired pre-pregnancy	First trimester	Second trimester	Third trimester
Cases (no.)	37	23	17	38
Disseminated	17 (0.46)	5 (0.23)	10 (0.59)	26 (0.68)
Fatalities	1 (0.03)	3 (0.14)	6 (0.35)	18 (0.47)

Peterson et al, 1993 – review of literature (71 cases) plus 41 additional cases

Pregnancy and immunity

- Pregnancy is considered to be a state of relative immunodeficiency
 - rheumatoid arthritis improves
 - DTH & in vitro measures of immunity decline
- However, most women are healthy during pregnancy
- Some infectious diseases have been reported to be more frequent during pregnancy
 - Tuberculosis
 - Listeriosis
 - Influenza
 - Coccidioidomycosis

Coccidioidomycosis is unique among fungal diseases in being more severe during pregnancy

- No evidence for other endemic mycoses
 - histoplasmosis
 - blastomycosis
 - cryptococcosis
 - paracoccidioidomycosis
 - sporotrichosis

Effect of sex hormones on coccidioidal growth

- 17 β -estradiol increased spherule growth & maturation and mycelial growth
 - *Coccidioides* binds to 17 β -estradiol, progesterone, & dihydrotestosterone
 - No binding by *Paracoccidioides*, *Blastomyces*, *Cryptococcus*, or *Candida*
 - no effect of 17 α -estradiol, cholesterol, & ergosterol
- No growth effects on *Cryptococcus*, *Candida*, *Pseudallesheria*

Drutz et al. Infect Immun 1981; 32:897

Drutz et al. J Infect Dis 1983; 147:372

Azoles and Pregnancy

Azoles and Pregnancy

- In 1992, an infant with congenital abnormalities born to a mother with coccidioidal meningitis who had been on fluconazole 400 mg during her entire pregnancy was reported
 - hypoplasia of nasal bones, cleft palate, craniosynostosis, humeral-radial fusion
- Similar to the Antley-Bixler syndrome

Azoles and Pregnancy

Since then, there have been 4 other cases, including a second child of the mother in the first case

Case	Time of treatment during gestation	Fluconazole dose
Lee, et al 1992	0-23 weeks	400 mg/day
Pursley, et al 1996	0-7 weeks, 9weeks-term	800 mg/day
Pursley, et al 1996	0-19 weeks	400 mg/day
Aleck and Bartley, 1997	0-4 weeks, 4-9 weeks, 22 weeks-term	400 mg/day, 800 mg/day, 1200 mg/day
Lopez-Rangel and Van Allen, 2005	0-23 weeks, 27 weeks-term	800 mg/day

ABS-like syndrome in infant born to mother on high-dose fluconazole



Patient at birth with “pear-shaped” nose, “dysplastic” ears, exorbitism, and synostosis at elbows



Radiographs at birth showing radiohumeral synostosis

Azoles and pregnancy

- Experimental administration of fluconazole to rodents results in congenital abnormalities when given early in gestation
 - Rat embryos 9.5 days of age were incubated in fluconazole 62.5 - 500 μ M & examined after 48 hr
 - Abnormalities occurred in the branchial arches
 - Menegola et al. *Repro Tox* 2001; 15:421
 - 50% of fetuses from CD1 pregnant mice given 700 mg/kg fluconazole on gestational day 10 developed cleft palate
 - Tiboni & Giampietro, *Ped Res* 2005; 58:94

Azoles other than fluconazole

- Similar abnormalities in rodent models have been observed with itraconazole, posaconazole and voriconazole
- There is no reason to consider them as less risky than fluconazole
- Voriconazole may be more teratogenic as it causes fetal abnormalities at less than therapeutic doses
 - assigned FDA Pregnancy Class D

Antley-Bixler Syndrome (ABS)

- Described in 1975
 - cranial synostosis, mid-face hypoplasia, proptosis, frontal bossing, dyplastic ears, radial-humeral synostosis, choanal atresia
- Most cases are sporadic, some of autosomal recessive inheritance
- Some cases associated with mutations in cytochrome P450 oxidoreductases (POR)
 - leads to abnormalities in sterol metabolism

Postulate

- Fluconazole, and other azole antifungals, inhibit fungal 14 α -demethylase in the ergosterol pathway
- They also may inhibit similar enzymes in the mammalian cholesterol pathway
- When given early in pregnancy at high dose, azole antifungals may induce an Antley-Bixler syndrome
 - Aleck & Bartley, Am J Med Genet 1997; 72:253
- Alternatively, mothers with POR mutations may not appropriately metabolize azole antifungals and so develop teratogenic levels
 - Flück et al, Nat Genet 2004; 36:228

Are azole antifungals safe after the 1st trimester?

- Krcmery et al reported no fetal abnormalities in a pregnancy where the mother received 600 mg daily fluconazole for 21 days starting week 14
 - *Pediatr Infect Dis J* 1996; 15:841
- Campomori & Bonati found no congenital abnormalities among 16 women receiving a median of 291 mg fluconazole during the 2nd trimester
 - *Ann Pharmacother* 1997; 31:118
- Several papers have described lower dose fluconazole given during the 1st trimester without evidence of increase risk of congenital abnormalities

Management issues

Questions

- Should azoles be used at all during pregnancy?
 - Are they safe after the 1st trimester?
- What do we advise women with coccidioidomycosis about pregnancy?
- What is the best way to manage coccidioidal meningitis during pregnancy?

Three scenarios

- Women with prior coccidioidomycosis not requiring antifungal therapy who become pregnant
- Women with prior coccidioidomycosis requiring antifungal therapy who wish or are pregnant
 - non-meningeal
 - meningeal
- Women who develop coccidioidomycosis during pregnancy
 - first trimester vs second or third trimester
 - meningeal vs non-meningeal

Recommendations

Scenario #1

- Women with a history of prior coccidioidomycosis not currently requiring therapy
 - They are at low risk for developing problems during pregnancy
 - Close follow-up is advised
 - clinical and serologic evaluation every 6-8 weeks
 - treatment is not recommended

Scenario #2 - A

- Women of child-bearing potential on azole therapy for non-meningeal coccidioidomycosis
- They should be advised of the risks of continuing azole therapy if they become pregnant
 - they should be advised to consider birth-control measures
 - if they are planning on becoming pregnant, the azole therapy should be discontinued prior to conception
 - observe without therapy
 - clinical and serological evaluation every 6 weeks
 - or use IV amphotericin B

Scenario #2 - B

- If a woman on azole therapy for coccidioidal meningitis becomes pregnant
 - azole therapy should be stopped
 - start intrathecal (IT) amphotericin B
 - or observe without therapy
 - clinical and serological evaluation every 6 weeks

What about after the first trimester?

- After the 1st trimester, it appears reasonable to restart azole antifungal therapy in cases that require therapy
 - voriconazole should be avoided

Scenario #3 - A

- A woman develops non-meningeal coccidioidomycosis during the first trimester
 - observe
 - or start IV amphotericin B if disease is severe or disseminated

Scenario #3 - B

- A woman develops coccidioidal meningitis during the first trimester
 - consider IT amphotericin B

After the first trimester

- It is reasonable to use an azole antifungal
 - voriconazole should be avoided

Advice on case presented

- Woman with cutaneous coccidioidomycosis on itraconazole who wishes to become pregnant
 - Stop itraconazole prior to conception
 - Observe without therapy
 - follow every 6 weeks for clinical and serological evidence of disease
 - if disease recurs, start IV amphotericin B
 - after the 1st trimester, restart itraconazole