

Coccidioidomycosis During Pregnancy: A Review and Recommendations for Management

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Pregnancy is an established risk factor for the development of severe and disseminated coccidioidomycosis, particularly when infection is acquired during the later stages of gestation. Although recent studies suggest that the incidence of symptomatic coccidioidomycosis during pregnancy is decreasing and that outcome has improved, management is complicated by the observations that azole antifungal agents can be teratogenic when given to some women, particularly at high doses, early in pregnancy. This article summarizes the data on these issues and offers guidance on the management of coccidioidomycosis during pregnancy.

OVERVIEW OF PREGNANCY AND COCCIDIOIDOMYCOSIS

Pregnancy is one of the most commonly identified risk factors for the development of severe and disseminated coccidioidomycosis. This risk was apparent from the first published case reported by Farness in 1941 [1]. Smale and Birsner completed the first review of cases in 1949 and noted that 3 of the 4 maternal deaths among 2140 pregnancies in Kern County, California, were due to coccidioidomycosis [2]. In 1951, Vaughn and Ramirez [3] provided a more detailed description, focusing on 28 instances of coccidioidomycosis during 1946–1949 among 25328 pregnancies in Kern County, yielding a rate of 11 cases per 10000 pregnancies. They describe the increasing risk of severe disease when infection is acquired during late pregnancy. The next case series noted that, among 33736 live births during 1950–1967 at Kern County General Hospital, there were 26 cases of coccidioidomycosis, for a rate of 7.7

cases per 10000 pregnancies [4]. All 8 women without dissemination survived, whereas 6 (33%) of the 18 women with dissemination died. They also showed that treatment with amphotericin B improved outcome.

A large survey was performed by Wack et al [5] in Tucson, Arizona, in 1988. By reviewing the records of 3 delivery centers in the city, they found 10 cases of coccidioidomycosis among 47120 deliveries, for a rate of 2.1 cases per 10000 term pregnancies. All 7 women who developed coccidioidomycosis before the third trimester survived. Some of these women received ketoconazole, and this is the first report describing the use of an azole antifungal for coccidioidomycosis during pregnancy. Two women developed severe respiratory disease during the postpartum period and subsequently developed meningitis. A third developed illness during the first week postpartum and recovered. There were 8 deliveries, and all infants were healthy.

Caldwell et al [6] reviewed 32 pregnant women with coccidioidomycosis during the 1993 epidemic of coccidioidomycosis in Kern County, California. Disseminated disease occurred in 3 women. Twenty-five women had normal vaginal deliveries. Nine women received antifungal therapy, 5 of whom received intravenous amphotericin B during pregnancy and 4 of whom received azole antifungals postpartum. Twelve (38%) of the 32 cases were diagnosed during the third trimester. There were no maternal deaths.

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Arsura et al [7] examined the role of cellular immunity, as surmised by the development of erythema nodosum, among 61 pregnant women with coccidioidomycosis. They found no cases of disseminated coccidioidomycosis among 30 women who developed erythema nodosum, compared with 11 cases of dissemination among 31 who did not have this manifestation. Moreover, 97% of women with erythema nodosum recovered, compared with only 55% without it.

In addition to these series reports, there have been numerous individual case reports [8–19], including that of Mongan [20] of a particularly rapid demise because of respiratory failure. Two case reports contain extensive reviews of the literature [21, 22], and there is a recent general review [23]. Taking these case series and individual reports into account, there are several conclusions that may be drawn regarding the current status of coccidioidomycosis during pregnancy.

Conclusions Regarding Coccidioidomycosis Occurring During Pregnancy

First, the later the acquisition of coccidioidal infection during pregnancy, the more severe the maternal disease [2, 3, 5, 21, 22], with the greatest severity occurring during the immediate postpartum period [1, 2, 5, 12]. This phenomenon has recently been suggested by Singh and Perfect [24] to be an immune response inflammatory syndrome. Second, the rate of cases appears to be decreasing [2, 3, 5], although the reasons for this are unclear. One explanation could be publication bias in the early reports. Third, therapy with amphotericin B given to the mother has resulted in marked clinical improvement in many cases [11, 15, 16, 21, 22]. The number of women using azole antifungals during pregnancy is too small to make a conclusion. Finally, black race has been mentioned as a potential risk factor for worse disease [3, 7]. Although most cases have been described in white women, the population was predominantly white [5].

There are few reports specifically on the effect of pregnancy among women who acquired coccidioidomycosis before becoming pregnant. However, accepting that skin test reactivity to coccidioidin is evidence of prior coccidioidal infection [25], data suggest that reactivation in patients without active disease is uncommon. For example, Vaughan et al [3] noted that, among 800 pregnant women in Kern County in the late 1940s, 40% were coccidioidin skin test positive at their first prenatal visit. There were no cases of coccidioidal dissemination during their subsequent pregnancy. Harris [12] identified 2 instances of disseminated coccidioidomycosis occurring during pregnancy among 10 women with prior non-disseminated infection. As the author indicates, this is likely an over estimation of the true risk, because there are many unrecognized instances of nondisseminated coccidioidomycosis in healthy women. During the late 1970s, Dodge et al [26] noted

that approximately one-third of the population of Tucson, Arizona, was skin test positive. During a later period, Wack et al [5] identified only 10 cases of active coccidioidomycosis during pregnancy in the same city, suggesting a very low risk of reactivation. Finally, in an unpublished review of patients who underwent coccidioidal serologic testing by one of the authors (DP), there were no cases of recurrent coccidioidomycosis during pregnancy among 17 women with prior non-disseminated infection. Among 6 women with prior disseminated coccidioidomycosis, 2 had recurrences during pregnancy that required antifungal therapy. On the basis of the aforementioned data, it can be concluded that women with a history of resolved pulmonary coccidioidomycosis have a minimal risk of reactivation during pregnancy, whereas women with a history of disseminated coccidioidomycosis have some risk of reactivation if they become pregnant.

NEONATAL OUTCOME

In older studies, there is evidence of fetal wastage and the delivery of low birth weight infants among women with active coccidioidomycosis during pregnancy [21]. However, other risks for poor fetal outcome were not detailed in these early studies, and the findings were not substantiated in a more recent review [5]; there is no recent evidence of fetal wastage or prematurity. Passive transfer of complement-fixing (IgG) antibody to the newborn occurs but does not indicate newborn infection [2, 17, 19, 27]. In addition, there have been at least 2 instances of passive transfer of IgM to newborns without evidence of active infection [28]. There are several case reports of neonates acquiring active coccidioidomycosis [29–35]. In most cases, the presentation is one of massive lung involvement, with high mortality and evidence of extrapulmonary involvement on autopsy. The route of infection in such cases has not been established. Because there are several reports describing involvement of the placenta without evidence of fetal involvement [3, 8, 19, 36, 37], it is presumed that congenital coccidioidomycosis does not occur and that neonatal cases represent aspiration of either amniotic fluid or vaginal secretions at the time of birth [37–39].

TREATMENT OF COCCIDIOIDOMYCOSIS DURING PREGNANCY

Amphotericin B was the first effective therapy for coccidioidomycosis [40]. However, its toxicity, restriction to an intravenous formulation, and lack of efficacy for coccidioidal meningitis, except when instilled directly into the cerebrospinal fluid, limited its usefulness. Ketoconazole was the first orally available azole antifungal used as therapy for coccidioidomycosis [41] but was soon supplanted by the triazole antifungals fluconazole and

itraconazole. Both had the advantage of efficacy for coccidioidal meningitis [42, 43].

Reports of Teratogenicity Associated With Azole Antifungals

However, soon after their introduction, data suggested that azole antifungals could be teratogenic. In 1992, a case report described congenital malformations in an infant born to a woman taking fluconazole during pregnancy. The mother had a history of disseminated coccidioidomycosis that developed during the third trimester of a previous pregnancy. She had received intrathecal amphotericin B but, after developing arachnoiditis, was enrolled in a fluconazole study in 1990. Later, while still receiving fluconazole, she became pregnant, notifying her doctors at 23 weeks gestation. At that time, an ultrasound revealed no abnormalities. She experienced premature labor at 27 weeks and delivered an infant with several dysmorphic features, including craniosynostosis, cleft palate, humeral-radial fusion, bowed tibia and femur, hypoplasia of the nasal bones, and short thumbs and toes [44]. The constellation of findings was similar to the Antley-Bixler syndrome, a rare congenital disorder of craniosynostosis and skeletal abnormalities first described in 1975 [45]. At the time, it was unclear whether the congenital defects could be attributed to fluconazole, but the presence of a rare constellation of defects in the presence of an exposure raised suspicion.

Since that time, 4 additional cases of infants delivered by mothers receiving fluconazole have been reported [46, 47], including a second infant delivered by the mother initially reported by Lee et al [48] (Table 1). All women received fluconazole at doses of ≥ 400 mg daily during the first trimester of pregnancy, and all but one was being treated for coccidioidal meningitis. On the other hand, several studies have reported a lack of congenital defects among infants delivered by women exposed to short courses of lower doses of fluconazole, including when given during the first trimester [49–51]. Recently, an observational study of itraconazole use for vaginal candidiasis

during pregnancy did not find a greater incidence of congenital abnormalities but did note an increased risk of spontaneous abortion among women receiving it [52].

Animal data suggest that the teratogenicity of fluconazole depends on the timing of the exposure. Pregnant mice given a single high dose (700 mg/kg) showed a peak incidence of cleft palate when exposed on the tenth day of gestation that rapidly decreased thereafter [53]. There are few data on safety of fluconazole after the first trimester in humans, but the reports that have been published suggest that exposure later in pregnancy may be safe. In one report, the daily use of 600 mg of fluconazole for 3 weeks, beginning at the 14th week of gestation, did not result in any infant malformations [54]. Campomori and Bonati [55] reported a series of 16 women with a median exposure to fluconazole in the second trimester. No congenital defects were observed; however, fluconazole use was limited to low-dose, short courses for vaginal candidiasis. There is a report of ketoconazole use for coccidioidomycosis starting in the second trimester without infant malformation [5]. Ketoconazole has also been used safely for treatment of Cushing syndrome during pregnancy, including during the first trimester [56, 57].

Possible Mechanisms of Teratogenicity Associated With Azole Antifungals

There are reasons to assume that azole antifungals may be associated with abnormal embryogenesis. In animal studies, administration of fluconazole to pregnant rats has been linked to branchial arch abnormalities in embryos [58, 59]. Moreover, azole antifungals inhibit human lanosterol 14- α demethylase, also known as CYP51, an enzyme required for steroidogenesis that is dependent on microsomal cytochrome P450 oxidoreductases (POR) for electron donation [60]. Animal models have demonstrated a critical role for POR-dependent sterol synthesis in limb and skeletal development [61], and at least some cases of Antley-Bixler syndrome have mutations in genes encoding for POR [62].

Therefore, it is possible that the craniofacial and skeletal abnormalities seen in the cases of fetal high-dose fluconazole exposure represent the severe end of a spectrum of malformations due to aberrant sterol metabolism [46]. Although lesser disorders of sterol metabolism have not been reported in epidemiologic studies of fluconazole exposure during pregnancy, there has been no specific search for them. Thus, the identified cases in the literature of severe malformations associated with fluconazole exposure may represent the tip of the iceberg in terms of the effects on the fetus. In addition, because POR is necessary for all cytochrome P450 enzymes, maternal POR mutations may alter drug metabolism. Flück et al [63] have suggested that, in some women with POR mutations, levels of fluconazole may reach teratogenic

Table 1. Details of the 5 Cases of Fetal Abnormalities Associated With Fluconazole Given During Pregnancy

Study	Time of fluconazole administration during gestation	Daily dose of fluconazole, mg
Lee et al (1992) [44]	0–23 weeks	400
Pursley et al (1996) [48]	0–7 weeks; 9 weeks until term	800
Pursley et al (1996) [48]	0–19 weeks	400
Aleck and Bartley (1997) [46]	0–4 weeks; 4–9 weeks, 22 weeks until term	400–1200
Lopez-Rangel and Van Allen (2005) [47]	0–23 weeks; 27 weeks until term	800

Table 2. Recommended Management of Coccidioidomycosis During Pregnancy

Clinical scenario	Suggested strategy	Alternatives strategies
No known infection but at risk		
All trimesters	Educate patient about signs and symptoms of coccidioidomycosis	
Distant infection (no active disease)		
All trimesters	Regular clinical follow-up including serial serological testing every 6–12 weeks	
Recent/active nonmeningeal infection		
1st trimester	Amphotericin-based regimen	If possible avoid azoles, consider clinical and serological monitoring
2nd–3rd trimester	Azole antifungals	Consider amphotericin-based regimen
Meningitis		
1st trimester	Intrathecal amphotericin	Azole antifungal ^a
2nd–3rd trimester	Azole antifungal ^a	Intrathecal amphotericin

^a Fluconazole or itraconazole (400 mg daily).

concentrations in the fetus. However, this has not yet been demonstrated.

Among the azole antifungals, fluconazole is not unique in its association with fetal abnormalities. Itraconazole [64] and posaconazole [65] have also been found to cause similar abnormalities in animal models. Although fluconazole, itraconazole, and posaconazole generally require high doses to cause such abnormalities, voriconazole has been associated with them at subtherapeutic doses and is currently listed as a class D agent for pregnancy by the Food and Drug Administration [66].

Azole Antifungals and Breastfeeding

There are few data on the use of azole antifungals during breastfeeding. It is known that both fluconazole and itraconazole enter breast milk, but no information is available for either posaconazole or voriconazole [67, 68]. In general, the concentration of drugs in breast milk is proportional to that in the maternal plasma [69]. The concentration of ketoconazole was estimated in a 41-year-old breastfeeding woman and found that the infant's exposure would be minimal [70]. Similarly, Force [71] measured the concentration of fluconazole in blood and breast milk over time after a single dose of

150 mg and found that ~85% of the plasma concentration was found in breast milk. This has been estimated to be less than concentrations for prescribed doses for neonates [69]. Similarly, itraconazole has been found to enter breast milk at low concentrations but may accumulate over time [67]. The American Academy of Pediatrics considers fluconazole to be compatible with breastfeeding [72], but women should not consider breastfeeding while receiving itraconazole [67], posaconazole, or voriconazole, for which there are no data [69].

CONCLUSIONS AND RECOMMENDATIONS

The aforementioned data led to a series of conclusions and recommendations regarding the management of coccidioidomycosis during pregnancy (Table 2). First, women with a history of coccidioidomycosis who do not have active disease appear to be at low risk for relapse during pregnancy. Because delayed type hypersensitivity testing with coccidioidin is not currently available, some of these women may be at greater risk for reactivation than others. At this time, cautious clinical follow-up, including serial coccidioidal serologic testing every 6–12 weeks, is recommended, but empirical antifungal therapy is not. Emergence of a positive serologic test result or an increasing titer would suggest reactivation of disease and consideration for therapy. In addition, it is reasonable to perform serologic testing for all pregnant women living in a region where coccidioidomycosis is endemic at their first antenatal visit. A positive test result would suggest active disease and would warrant further clinical evaluation. Coccidioidomycosis should be considered as an etiology for a febrile pulmonary illness in a pregnant woman either residing in a region where coccidioidomycosis is endemic or with an appropriate travel history.

More problematic is the woman who is receiving azole antifungal therapy and wishes to become pregnant. If the coccidioidomycosis is well controlled without meningeal involvement, one approach is to stop the azole antifungal therapy before conception and monitor the patient every 4–6 weeks during the first trimester for reactivation of disease. If that were to occur, treatment with intravenous amphotericin B is recommended, at least during the first trimester. If the woman is already receiving ≥ 400 mg daily of azole antifungal therapy at the time of diagnosis of pregnancy, for the first trimester, either the azole antifungal therapy could be discontinued with a change to intravenous amphotericin B, or with the mother's understanding of the potential risks, azole antifungal therapy could be continued.

More difficult is the woman with coccidioidal meningitis who wishes to become pregnant. Although stopping azole antifungal therapy before conception and changing to intrathecal amphotericin B is an option, another approach is to continue azole antifungal therapy with the mother educated about the

potential teratogenic risks. Finally, a third approach is to observe the mother without any antifungal therapy. However, the risk of relapse is significant [73], and this approach is not recommended.

Another issue is how to address management during the second and third trimesters. The reports of fetal abnormalities suggest that the effects of azoles are occurring early and that azole antifungal therapy should be safe after the first trimester. However, these data are limited. We believe that, after the first trimester, azole antifungal therapy is reasonably safe and can be cautiously recommended. However, many mothers and clinicians may feel more comfortable with using intravenous amphotericin B, and certainly, there are sufficient data to support its use for the treatment of coccidioidomycosis during pregnancy [11, 15, 16, 21, 22]. This topic is particularly problematic in the woman with coccidioidal meningitis, for which the only option other than oral azole antifungals is intrathecal amphotericin B [16].

Observations suggest that severe coccidioidomycosis is likely to occur during the postpartum period when infection is acquired during late pregnancy. Here, either an azole antifungal or amphotericin B is recommended, but the authors feel that, in severe cases, intravenous amphotericin B may be the initial treatment of choice, because of the clinical experience [11, 15, 16, 21, 22]. A subsequent change to an azole antifungal therapy can be made after the mother's condition stabilizes. As Crum notes [22], recommendations for therapeutic abortion based only on the presence of maternal coccidioidomycosis are no longer supported. Early inducement of labor should be considered in cases of either maternal or fetal distress, with vaginal delivery preferred. Decisions regarding these issues are best made by the attending obstetrician.

Current evidence indicates that neonatal infection is uncommon and is most likely acquired during delivery. Measurement of newborn serologic levels is not helpful in assessing this risk, and close clinical pediatric follow-up is advised. In addition, although it appears to be safe for mothers to breast-feed while receiving fluconazole, other azole antifungals should be avoided.

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