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Coccidioidomycosis in pregnancy: Case report and literature review of associated placental lesions

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ABSTRACT

Background: Coccidioidomycosis is an endemic fungal infection found most commonly in the Southwestern United States, Northwestern Mexico, and parts of Central and South America. Although infection is relatively uncommon during pregnancy, it is imperative to have an index of suspicion in order to diagnose and begin timely treatment to prevent dissemination and dire consequences.
Case report: A 33-year-old Hispanic female was evaluated after she was involved in an automobile accident. Radiographic evaluation showed a 3.2 × 3.2 cm cavitary thick-walled lesion. A biopsy was negative for malignancy. Evaluation was positive for coccidioidomycosis by complement fixation reaction. Four months later, the patient presented 7 weeks into a pregnancy with massive hemoptysis. Bronchoscopy revealed bleeding from the right upper lobe and emergency embolization was performed. The patient had a spontaneous abortion 9 days after admission. The right upper and middle lobes of the lung were resected due to continuous bleeding. A subsequent pregnancy was un-eventful. Coccidioidomycosis titers remained negative throughout the second pregnancy.
Discussion: This case demonstrates the potential for severe pulmonary coccidioidomycosis and vascular strain of pregnancy-associated vascular expansion in the first trimester of pregnancy and the possibility of a favorable pregnancy outcome in subsequent pregnancies after appropriate treatment. The route of feto-maternal transmission and placental lesions in coccidioidomycosis are discussed.

1. Introduction

Coccidioidomycosis also known as Valley Fever, is an infection caused by the fungi of the genus Coccidioides [1]. *Coccidioides* spp. are dimorphic, soil-dwelling fungi known to cause a broad spectrum of symptoms ranging from a mild febrile illness to severe pulmonary manifestations or disseminated disease [2,3]. The genus *Coccidioides* is comprised of two genetically distinct species: *C. immitis* and *C. posadasii* [4]. These two species cause similar clinical symptoms, however they are present in different geographic regions. *C. immitis* is found in central and southern California, with the San Joaquin Valley being the region of greatest endemicity [3]. The most concentrated region for *C. posadasii* is in Arizona and sporadic sites in southern Utah and Nevada. Outside the U.S., *C. posadasii* is present in parts of Mexico and Central and South America [3,4]. Cases of coccidioidomycosis in pregnancy are rare and were extensively described in a review by *Crum and Ballon-Landa* [5]. Maternal and fetal mortality, associated with the disseminated disease, is high. Medical pregnancy termination has been advised when disseminated infection is detected in early pregnancy [6,7]. Recent reports showed discrepancies between Coccidioidomycosis-related perinatal mobility and mortality and the disease-associated placental lesions. Here, we report a case of coccidioidomycosis in a woman with a non-viable pregnancy with a subsequent unaffected pregnancy and non-specific placental lesion. A literature review of placental findings associated with coccidioidomycosis cases, published since 1948, is provided.

2. Case report

A 30-year-old Hispanic female with an intrauterine pregnancy at 7 weeks of gestation was admitted to the hospital with mild

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hemoptysis, which evolved into massive bleeding during hospitalization. The patient was diagnosed with pulmonary coccidioidomycosis four months earlier. This initial diagnosis was made after a chest X-ray and CT scan performed due to trauma (car accident). The evaluation revealed a 3.2 × 3.2 cm thick walled cavitary lesion in the right upper lobe. A CT guided biopsy was performed and was negative for malignancy. Serum analyses of Coccidioides antibodies by Complement Fixation (CF) were positive (1:32). The patient was prescribed fluconazole, which she discontinued after two weeks. At the subsequent admission four months later, the patient complained of blood tinged sputum (20–35 ml at a time, 2–3 times per day) and productive cough for 3 days. She denied shortness of breath, night sweats, chills, fever, sore throat, chest pain, wheezing, loss of weight or appetite, and nausea or vomiting. The medical history was remarkable for a 15-years history of type I Diabetes Mellitus on insulin. The patient lived in West Texas and had no recent travel history. Her last PPD was 15 years prior with no history of TB exposure.

2.1. At physical examination

At the physical examination, the patient had a temperature of 98.7°F, a pulse rate 108 beats/min, systolic/diastolic BP of 146/92 mm Hg, and oxygen saturation of 97% on room air. The auscultation revealed coarse breath sounds over right upper lobe. Neither visible skin lesions, nor palpable lymph nodes were noted.

2.2. Laboratory data

The complete blood count showed leukocytosis (WBC 11.8 × 10^3 μl with polymorphs 72%), Hb 14.1 g/dl, platelet count of 279 × 10^3/μl, and an eosinophil count within the normal range. The complete metabolic panel was unremarkable, except Hb A1C was 9.3%. Urine analysis showed 12 WBC/hpf, 4 RBC/hpf, protein 50 mg/dl, 500 leucocytes/ul, and βhCG 8715 mIU/ml. Sputum cultures and smear were negative for acid-fast bacilli (AFB). A serum fungal panel was positive for coccidioidomycosis antibodies only. Coccidioidomycosis CF titer was 1:4, IgG 2:1, IgM 1:5. Chest radiography findings were unchanged compared to the prior radiograph. A transvaginal ultrasound showed an intrauterine pregnancy with a 6.5 week fetal pole with no fetal heartbeat.

2.3. Hospital course

Three days after admission, the patient's hemoptysis worsened (>240 ml/24 h), she developed sinus tachycardia and shortness of breath and was transferred to the ICU. A bronchoscopy revealed a localized hemorrhage in the right upper lobe and an emergency embolization of the right bronchial artery was performed. After the embolization, the patient's hemoptysis was temporarily controlled (20–30 ml/24 h). Fluconazole was initiated on the fourth day after a multidisciplinary discussion of optimal treatment. On the ninth day of the admission, the patient had a spontaneous abortion. The following day 60 ml expectoration of blood in one sitting was noticed. A right upper and middle lobe lobectomy was performed. The patient recovered and was subsequently discharged 16 days after admission. Oral fluconazole was continued at discharge. The patient received instructions to follow up regularly at an infectious diseases clinic as an outpatient and emphasis was placed on strict adherence to medication and contraception. Fluconazole was continued for one year. A follow up chest CT revealed no active lymph nodes or infiltrates. Eight months later, the patient became pregnant. Coccidioidomycosis antibody complement fixation titer remained negative throughout the pregnancy. An elective cesarean section was performed at 37 weeks (due to 2 previous cesarean sections) without any complications. The placenta was collected and evaluated.

2.4. Placental evaluation

2.4.1.

The placenta was collected after delivery and was either paraffin-embedded for immunohistochemistry or flash-frozen in liquid nitrogen for Quantitative Polymerase chain reaction (Q-PCR). DNA was isolated from the placenta tissues, membrane, and cord using a Wizard Genomic DNA Purification kit (Promega, Madison, WI, USA). The DNA samples were than analyzed using the absolute quantification real-time PCR method. Samples were run with FastStart Essential DNA Green Master mix (Roche, Indianapolis, IN, USA) and commercially available primers and controls: β-actin [8] and Coccidioides species [9]. The assays were performed in triplicate. A standard curve was prepared from dilutions of a *Coccidioides immitus* control DNA (Vircell, Granda, Spain). The dilutions used to make the standard curve were 60,000 copies/rxn, 6000 copies/rxn, 600 copies/rxn, and 60 copies/rxn. The placental tissue samples were negative for *Coccidioides immitus* DNA (Fig. 1).

2.4.2. Pathological evaluation

The placental weight was 500 g. Pathological evaluation of the placenta revealed foci of calcification (Fig. 2A), increased number of syncytial knots (Fig. 2B), edematous villi (Fig. 2C) and necrosis (Fig. 2D).

3. Discussion

Coccidioidomycosis is caused by *Coccidioides immitis or C. posadasii*, endemic to the Southwestern United States, northwestern parts of Mexico, Central and South America [10]. The exact incidence of coccidioidal infections is difficult to calculate because approximately 60% of infected individuals are asymptomatic or have subclinical disease and never seek medical attention. An estimated 150,000 infections occur annually in the United States [11]. The incidence of coccidioidal infections in Arizona, Nevada, California, New Mexico, and Utah has increased from 5.3 per 100,000 in 1988 to 42.6 per 100,000 in 2011 [12]. Around 75,000 deaths per year result from the infection. This increase in the disease occurrence requires particular attention in the pregnant population, since the consequences could manifest not only in the dissemination of coccidioidomycosis, but also result in fetal disease, congenital anomalies and other developmental sequels [5]. Despite the fact that coccidiomycosis has been more common among men than women (55–66% of cases collected from surveillance data from Arizona (1993–2006) involved men), pregnant women experience dissemination 40–100 times more frequently than men [13–15]. Pregnancy alters the maternal immune system which potentially increases maternal and fetal vulnerability to common viral and parasitic infections [16]. The consequences could be far greater for women, than for men. The usual route of *Coccidioides* transmission is through inhalation of spores that are found in the soil of endemic areas. Spores get lodged in the lungs and produce spherules [17]. After infection, a wide spectrum of manifestations is possible. Early symptoms such as cough, fever, and arthralgia are fairly common. Primary infections most commonly manifest as community-acquired pneumonia approximately 7–21 days after exposure. Complications of coccidioidomycosis include severe pneumonia with respiratory failure and bronchopleural fistulas requiring resection, lung nodules, and dissemination. Dissemination may be rapid with fatal consequences. Any organ of the body can be involved in dissemination, but *Coccidioides* species have an affinity for the lungs, skin, soft tissue, joints, brain, and especially the meninges. Hemoptysis may occur and suggests the development of a pulmonary cavity. Cavities present in approximately 2 to 8% of adults infected with a *Coccidioides* species. Pregnant women are at a higher risk for dissemination and re-activation of the infection [18], however not all pregnant women who develop coccidioidomycosis are at risk for dissemination – Wack et al. [3] reported only 10 cases of coccidioidomycosis in 47,120 pregnancies in an endemic area of Arizona in 1988 (2.1 cases per 10,000 pregnancies). Only 2

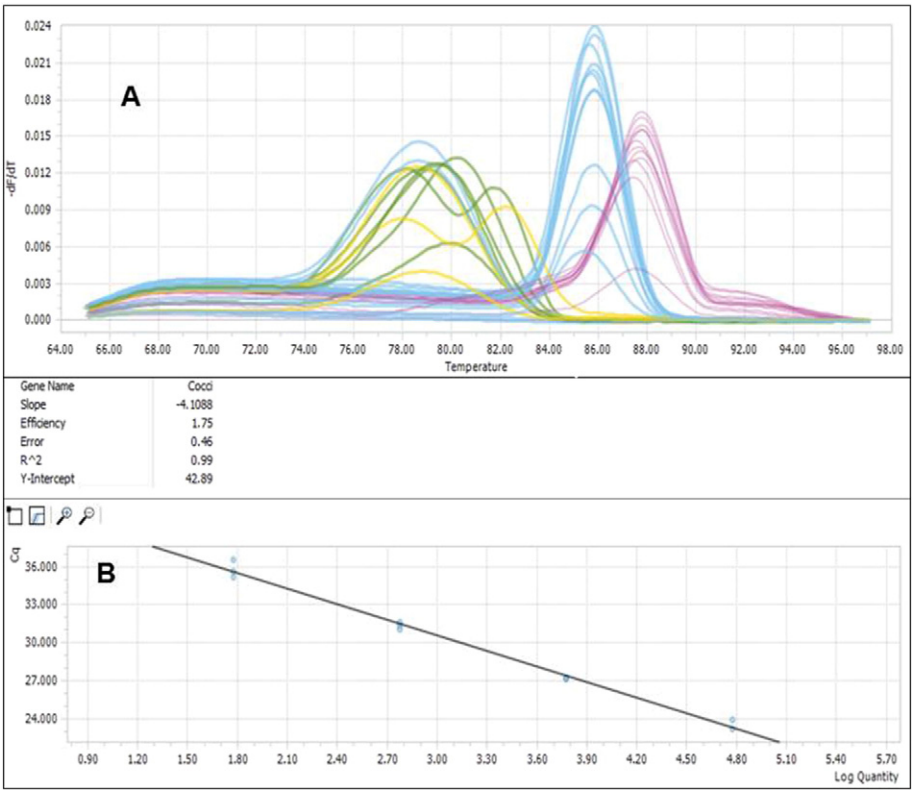

Fig. 1. A. Melting curve for β-actin (pink color, melting temperature 87.5 °C) and Coccidioides spp. (blue color, melting temperature 85.5 °C.) in the control DNA samples, placental samples (placenta, attached to placenta umbilical cord, fetal membranes) and soil samples. Note: placental samples do not show specific amplification. **B**. Standard curve for quantifying Coccidiosis spp. that was created by using 4 standards with the following dilutions: 60,000 copies/rxn, 6000 copies/rxn, 600 copies/rxn, and 60 copies/rxn.

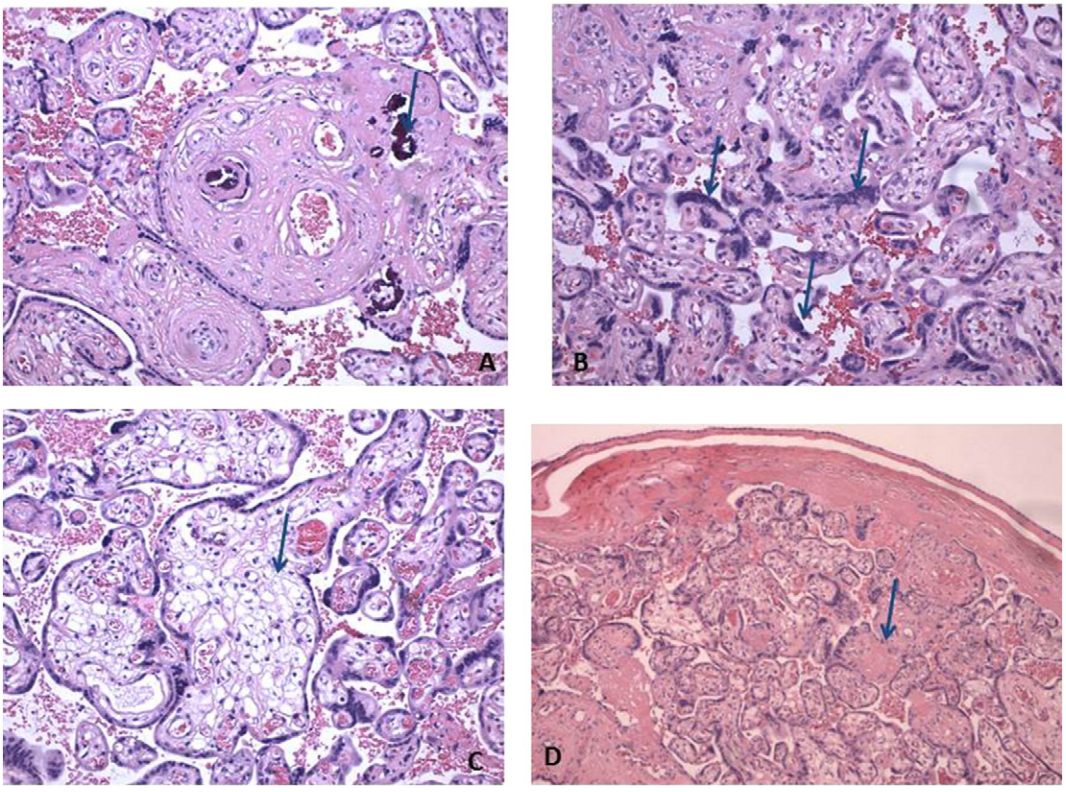

Fig. 2. (A) Microphotographs of the placenta, demonstrating villous calcification shown at 100× magnification, (B) increased number of syncytial knots shown at 100× magnification, (C) edematous villi shown at 100× magnification, and (D) necrosis (arrows) shown at 40× magnification.

Table 1
Reported in the literature cases of coccidioidomycosis with available information regarding placental evaluation in human and animal studies.

Age	Time of Diagnosis	Disseminated sites of disease in article	Titer	Treatment	Fetal outcome	Placenta gross and micro description	Maternal outcome	Geographic area	Strain	Reference
20	Day of delivery	Yes	1:64	Amphotericin B, postpartum	Infected infant	Multiple foci of acute inflammation with numerous *Coccidoides* spherules.	Fatal	San Francisco, CA	*C. Imittis*	[18]
38	34 weeks	Disease reactivation during pregnancy	1:04	Amphotericin IV	Healthy infant	Normal placenta, weighed 310 g at 36 weeks.	Recovered	NR	*C. Imittis*	[17]
30	18–19 weeks	NR	1:16	Fluconazole	Healthy infant	Unremarkable	Recovered	Recent travel to Arizona and Mexico	*C. Imittis*	[6]
N/A	N/A	N/A	N/A	N/A	N/A	16 cases of placentitis in association with 35 cases of maternal death	Fatal	N/A	N/A	[19]
34	16 weeks	During pregnancy	NR	NR	Fetal death	Many caseous areas scattered through the placenta, otherwise there were no lesions.	Fatal, 20 weeks gestation	California	NR	[21]
22	20 weeks	During pregnancy	NR	NR	Premature birth, death at age 1 month	Necrotic, purulent and caseous lesions, filled with spherules, some large spherules contained encapsulated endospores. No inflammatory lesions were in the umbilical cord.	Fatal, two weeks after birth	Kern County, CA	*C. imittis*	[21]
NR	30 weeks	During pregnancy	NR	Daily amphotericin B	Healthy infant	Placental weighed 530 g, several small intravenous thrombi, and minor areas of necrosis those were firm. These white areas contained dead villi enmeshed dense fibrin deposits and isolated edematous reactions to *Coccidioides*. Numerous typical *Coccidioides* were present without inflammatory proliferation.	Labor induced	Area endemic for Coccidioides	NR	[22]
34	24 weeks	Two years prior to pregnancy	1:256 after delivery	Daily amphotericin B	Healthy infant	Occasional necrotic foci with *Coccidioides*	Recovered	Contracted in Arizona	NR	[22]
30	20 weeks	Diagnosed during pregnancy	NR	NR	Fetal death	Zones of necrosis, subacute inflammation. The zones in which spores were found are localized by heavy deposit of fibrin and blood platelets, filling the intervillous space. Within this zone, chorionic villi were necrotic, but those with *C. Imittis* spherules were viable. Ephithelioid and giant cell reaction.	Fatal	Wyoming, Colorado	*C. Imittis*	[23]
N/A	Third trimester	N/A	N/A	N/A	N/A	Placentas were infected with coccidioidomycosis in all 6 cases of maternal death	Fatal	N/A	N/A	[24]
34	Preterm birth	During pregnancy	NR	NR	Twins; one died at age 11 days, the other died at age 21 days	No lesions	Fatal	Riverside, CA	NR	[25]
34	At term	During pregnancy	NR	NR	Healthy infant, titer 1:4	No granulomas	Reported with 4 cases of maternal	Kern County, CA	NR	[26]

							death			
20	16 weeks	During pregnancy	1:128	NR	Delivered by postmortem C-section, death after 10 h	Marked focal acute and chronic granulomatous inflammation containing spherules and endospores *Coccidioides immitis*.	Fatal	Arizona	*C. immitis*	[27]
27	Postmortem	During pregnancy	1:128	NR	Preterm labor, healthy infant	Placenta weighed 359 g, had necrosis, acute inflammation, presence of the spherules. The area between necrotic lesions was normal	Fatal	Arizona	NR	[28]
27	26 weeks	During pregnancy	NR	Amphotericin B, vancomycin, and voriconazole	Fetal death at 26 weeks	Coagulative necrosis of chorionic villi and an intense infiltration by neutrophils, lymphocytes, and plasma cells in the intervillous space. Spherules filled with round fungal endospores and scattered individual sporangiospores of *Coccidioides* were identified adjacent to areas of placental infarction. Fetal membranes and umbilical cord were without significant inflammation. A 500 ml retroplacental hemorrhage (abruption) was found at the time of emergent cesarean section.	Recovered	California	NR	[29]
34	20 weeks	During pregnancy	Actidone	NR	Healthy infant delivered at term, titer 1:2	No pathologic evidence of coccidioidal granuloma of the placenta	Recovered	NR	NR	[30]
22	20 weeks	NR	NR	NR	Death at age 6 weeks	Numerous large and small lesions, both in the decidua and in the chorionic villi. The lesions were necrotic, come appearing caseous, others frankly purulent. These lesions were filled with spherules of *Coccidioides immitis*. Spherules were of all sizes and stages of development. Some large spherules contained encapsulated endospores.	Fatal	Kern County, CA	*C. Immitis*	[30]
N/A	Third trimester	N/A	N/A	N/A	N/A	No description of granulomas in 11 cases of disseminated Coccidioidomycosis	N/A	Kern County, CA	N/A	[30]
38	32 weeks	NR	NR	NR	Healthy infant, weighed 2381 g.	Grossly normal, at microscopic examination contained *Coccidioides immitis*.	Fatal	NR	*C. Immitis*	[31]
22	18 weeks	During pregnancy	1:128	Amphotericin B lipid complex (ABLC)	Premature birth at 25 weeks, had coccidioidomycosis, died at age 34 days	Multiple granulomas and large numbers of *Coccidioides* organisms. Abundant numbers of *C. Immitis* grew from placental and cervical cultures.	Recovered	Long Beach, CA	*C. Immitis*	[32]
21	24 weeks	During pregnancy	NR	Metacortin	Fetal death at 24 weeks in utero	Normal placenta	Fatal	Fort Bliss, TX	*C. Immitis*	[33]
21	28 weeks	During pregnancy	NR	Amphotericin after delivery	Healthy infant delivered preterm at 32 weeks	Normal placenta	Fatal	New Orleans, moved from Arizona	*C. Immitis*	[34]
37	24 weeks	During pregnancy	1:8	Amphotercin B	Healthy infant delivered at 38 weeks	Three areas of infarction (<2 cm in diameter), moderate intervillous fibrin deposition, numerous fungal spherules containing endospores and foreign body giant cells, acute inflammatory reaction, focal infarction with necrosis.	Recovered	New Mexico	NR	[35]
19	37 weeks	During pregnancy	NR	NR	Healthy infant, labor induced at 37 weeks	Multiple coccidioidomycosis micro-abscesses	Fatal	Central California	NR	[4]
Animal report										
N/A	N/A	Alpaca (*Vicugna pacos*)	1:256	N/A	Death	Many irregular, roughly round (~1–2 cm diameter) areas of hyperemia and hemorrhage covered by a fibrinous exudate on the chorionic and allantoic surfaces.	Euthanized	Southern California	N/A	[20]

of the 10 patients developed systemic illness that presented as fevers, pulmonary infiltrates and meningitis.

In a recent study of 32 cases of coccidioidomycosis in pregnant women residing in Kern County, California, dissemination developed in 3 women [19]. The risk of dissemination increases as the weeks of gestation advance, with the third trimester and immediate postpartum period having the highest risk. The mechanism of increased risk might be associated with depressed cellular immunity or changes in 17β-estradiol and progesterone levels, which enhance the maturation and growth of *C. immitis* [20–22]. The question regarding the transplacental passage of the spherules is controversial [23–26]. The spherules were found in the placenta (Table 1) and documented to destroy the villi, however sporules were not found in fetal circulation [20]. The pathognomonic features of coccidioidomycosis in the placenta and the absence of inflammatory response were described by McCafee and Benirschke [20]: "Coccidioides organisms were located in occasional microscopic foci of necrosis without inflammatory cell proliferation. Although this kind of bland necrotizing change is also characteristic of herpes simplex placentitis, the two diseases are differentiated by the morphologic features of the respective organisms." Taking into consideration multiple placental lesions, found in the cases of maternal coccidiomycosis, it was suggested that placental insufficiency might contribute to fetal demise [27]. In the reviewed cases of placental lesions, acute placental inflammatory response was reported in three cases with the fatal outcome. Increased fibrin deposition is a common placental lesion associated with this disorder (Table 1).

This fibrin deposition is part of the pathogenesis of coccidiomycosis: a fibrillar material, released by endospores, inhibits polymorphonuclear cell access to the emerging endospores [28]. The non-permissiveness of the placenta to coccidiomycosis was also explained by the characteristic thrombotic segregation of the organism, which may "eliminate viable capillaries" and thus prevent transmission to the fetus [29,30]. The placental lesions described in present case where non-specific for coccidiomycosis.

While the causative relationship between coccidioidomycosis and pregnancy loss cannot be determined, *Coccidioides posadasii and immitis* has been associated with abortion in animal examples [27,31]. African Americans, Filipinos, and Hispanics are known to be at higher risk for dissemination. In the present case, the patient had at least three risk factors making her more susceptible to a severe form of infection – Hispanic race, pregnancy, and diabetes. Treatments for coccidioidomycosis depend on the severity of the disease, presence of dissemination, and the site involved. Amphotericin B deoxylate, azoles, or both are available as treatment options. Amphotericin B deoxylate is considered to be the safest during pregnancy (category B). Lipid preparations of Amphotericin B are preferred over amphotericin deoxylate due to reduced toxicity. Azoles have been used as treatment for coccidioidomycosis for over 20 years, however soon after their introduction it became evident that Azoles might be teratogenic [32]. Currently, fluconazole is a category D drug. The patient in the presented case was reinitiated on fluconazole as her pregnancy was considered to be nonviable during her admission at early gestation, indeed this pregnancy resulted in spontaneous abortion.

Women with a history of resolved pulmonary coccidioidomycosis have a minimal risk of disease reactivation during pregnancy, whereas in women with a history of disseminated coccidioidomycosis this risk is increased [18]. In agreement with the later observation, in the presented case the second pregnancy was not associated with reactivation of the disease and placental lesions were nonspecific for coccidioidomycosis.

In conclusion, the described case demonstrates the potential for severe pulmonary coccidioidomycosis and vascular strain of pregnancy-associated vascular expansion in the first trimester of pregnancy and the possibility of a favorable pregnancy outcome in subsequent pregnancies after appropriate treatment.

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