Coccidioidomycosis in Pregnancy: Case Report and Literature Review of Associated Placental Lesions

TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER™ *at the* Permian Basin

Heliose Labuschagne[1], C. Burns[2], Stacy Martinez[3], Maira Carrillo[4], Melissa Waggoner[4], Irene Schwanninger[3], James Maher[4], Moss Hampton[4], Javier Flores-Guardado[1], and Natalia E. Schlabritz-Loutsevitch[4]

[1]Department of Internal Medicine, Texas Tech University Health Sciences Center at the Permian Basin, Odessa, TX; [2]Department of Pathology, Medical Center Hospital, Odessa, TX; [3]Department of Academic Affairs, Texas Tech University Health Sciences Center at the Permian Basin, Odessa, TX; [4]Department of Obstetrics and Gynecology, Texas Tech University Health Sciences Center at the Permian Basin, Odessa, TX

Introduction

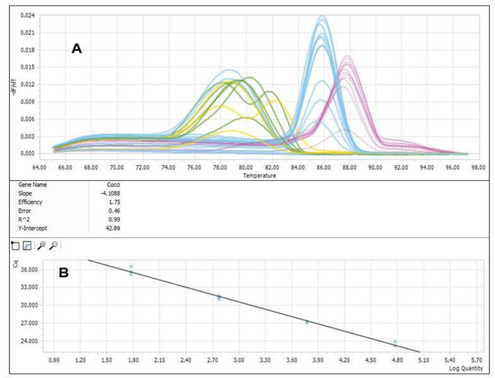
Coccidioidomycosis also known as Valley Fever, is an infection caused by the fungi of the genus Coccidioides. *Coccidioides spp.* are dimorphic, soil-dwelling fungi known to cause a broad spectrum of symptoms ranging from a mild febrile illness to severe pulmonary manifestations or disseminated disease. Cases of coccidioidomycosis in pregnancy are rare and were extensively described in a review by *Crum and Ballon-Landa*. 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.

Case Report

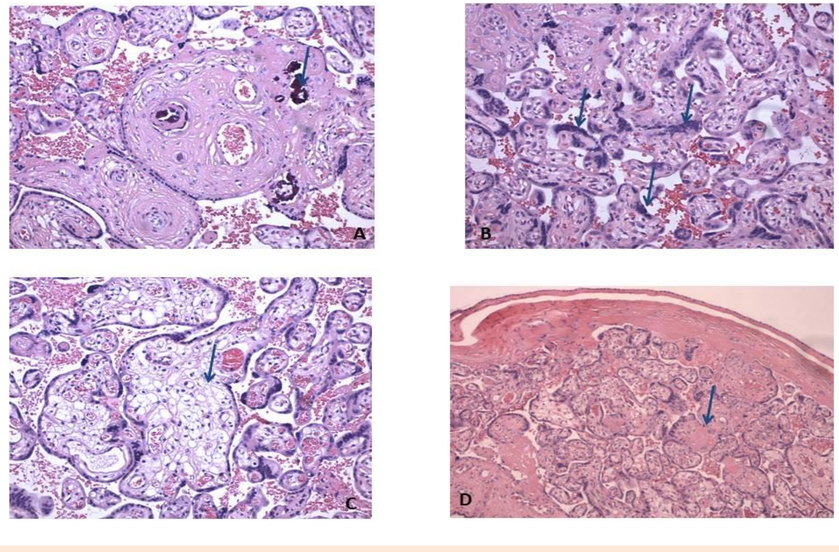
A 30-year-old Hispanic female with a 7-week intrauterine pregnancy was admitted to the hospital with mild hemoptysis, which evolved into massive bleeding during hospitalization. She was diagnosed with pulmonary coccidioidomycois four months earlier. This initial diagnosis was made after radiography performed due to a car accident. The evaluation revealed a 3.2 x 3.2cm thick walled cavitary lesion in the right upper lobe. 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. The medical history was remarkable for a 15-year history of type I Diabetes Mellitus on insulin. The patient lived in West Texas and had no recent travel. Her last PPD was 15 years prior with no history of TB exposure.

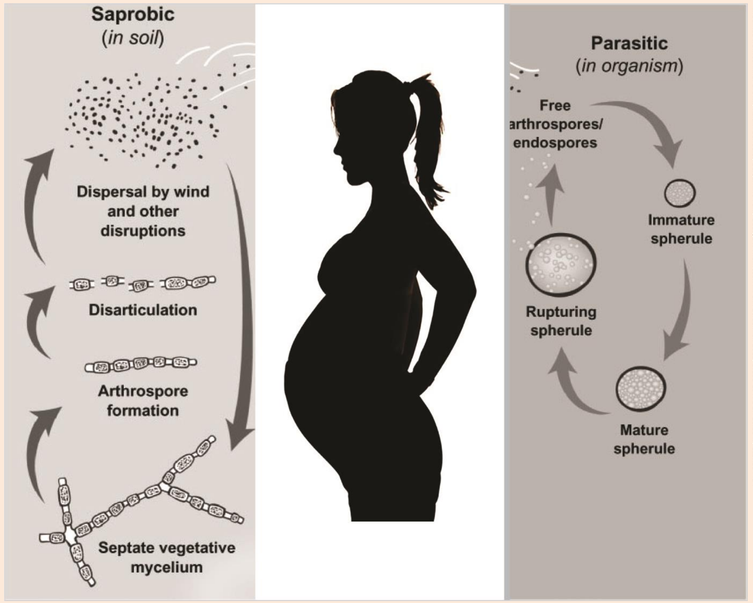
BELOW: Cases of coccidioidomycosis with available information regarding placental evaluation in human and animal studies reported in literature.

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. Immitis	[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. Immitis	[17]
30	18-19 weeks	NR	1:16	Fluconazole	Healthy infant	Unremarkable	Recovered	Recent travel to Arizona and Mexico	C. Immitis	[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. immitis	[21]
NR	30 weeks	During pregnancy	NR	Daily amphotericin B	Healthy infant	Placental weighed 530 g, several small intervillous 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. Imitis spherules were viable. Epithelioid and giant cell reaction.	Fatal	Wyoming, Colorado	C. Imitis	[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 death	Kern County, CA	NR	[26]
20	16 weeks	During pregnancy	1:128	NR	Delivered by postmortem C-section, death after 10 hours	Marked focal acute and chronic granulomatous inflammation containing spherules and endospores Cocci-cloides 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. Immits grew from placental and cervical cultures.	Recovered	Long Beach, CA	C. Immits	[32]
21	24 weeks	During pregnancy	NR	Metacortin	Fetal death at 24 weeks in utero	Normal placenta	Fatal	Fort Bliss, TX	C. Immits	[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	Amphotericin 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 coccidiodo-mycosis 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]



LEFT: (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, 6,000 copies/rxn, 600 copies/rxn, and 60 copies/rxn. **RIGHT:** (A) Microphotographs of the placenta, demonstrating villous calcification shown at 100x magnification, (B) increased number of syncytial knots shown at 100x magnification, (C) edematous villi shown at 100x magnification, and (D) necrosis (arrows) shown at 40x magnification.





Modified from Jennifer Brown, Kaitlin Benedict, Benjamin J Park, George R Thompson III. Clin Epidemiol. 2013; 5:185-197. DOI: 10.2147/CLEP.S34434

At the physical examination, she had a temperature of 98.7°F, a pulse rate 108 beats/min, systolic/diastolic BP of 146/92, and oxygen saturation of 97% on room air. The auscultation revealed coarse breath sounds over right upper lobe.

The complete blood count showed leukocytosis (WBC 11.8 x 10^3µL with polymorphs 72%), Hb 14.1 g/dl, platelet count of 279X10^3/µl, and an eosinophil count within the normal range. The complete metabolic panel was unremarkable, her 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.

Three days after admission, the patient's hemoptysis worsened (>240ml/24h), 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 (20-30ml/24h). 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. 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. Fluconazole was continued for one year. 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 without any complications.

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 then 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, 6,000 copies/rxn, 600 copies/rxn, and 60 copies/rxn. The placental tissue samples were negative for *Coccidioides immitus* DNA.

The placental weight was 500g. Pathological evaluation of the placenta revealed foci of calcification, increased number of syncytial knots, edematous villi and necrosis.

Discussion

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. 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. This increase in 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]. Complications of coccidiodomycosis include severe pneumonia, lung nodules, and dissemination. 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. Pregnant women are at a higher risk for dissemination and re-activation of the infection, however not all pregnant women who develop coccidioidomycosis are at risk for dissemination.

The pathognomonic features of coccidioidomycosis in the placenta and the absence of inflammatory response were described by McCafee and Benirschke: "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."

Women with a history of resolved pulmonary coccidioidomycosis have minimal risk of disease reactivation during pregnancy, whereas in women with a history of disseminated coccidioidomycosis this risk is increased. As such, in the presented case the second pregnancy did not see disease reactivation and placental lesions were nonspecific for coccidiodiomycosis.

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.

Laura W. Bush INSTITUTE for WOMEN'S HEALTH
TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER
ANGELO STATE UNIVERSITY