Brucellosis in pregnancy: a case report

Alexis M. Dunn[1], Laura E. Coats[2], Tulip A. Jhaveri[3], Kamir Boodoo[3], Samantha Williams[3], Elizabeth A. Lutz[2], Sarah Araji[2]^

[1]Department of Medical Education, University of Mississippi Medical Center, Jackson, MS, USA; [2]Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of Mississippi Medical Center, Jackson, MS, USA; [3]Department of Infectious Disease, University of Mississippi Medical Center, Jackson, MS, USA

Contributions: (I) Conception and design: TA Jhaveri, K Boodoo, S Williams, EA Lutz, S Araji; (II) Administrative support: LE Coats, EA Lutz, S Araji; (III) Provision of study materials or patients: AM Dunn, TA Jhaveri, K Boodoo, S Williams, S Araji; (IV) Collection and assembly of data: AM Dunn, LE Coats, TA Jhaveri, K Boodoo, S Williams, S Araji; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sarah Araji, MD, MS. Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216, USA. Email: saraji@umc.edu.

Background: *Brucella* spp., a gram-negative bacterium, is one of the most prevalent zoonotic illnesses worldwide and is more commonly seen in animals; however, the disease may be present in humans. Clinical manifestations of brucellosis are variable and can range from asymptomatic to severe disease. In women who are pregnant, potential obstetrics complications are possible. The purpose of this report is to present a case of brucellosis in a pregnant patient and discuss the potential complications and treatment recommendations.

Case Description: We present a case of a 17-year-old gravida 2, parity 1 (G2P1) at 35 weeks and 2 days (35w2d) with brucellosis after she assisted in the delivery of puppies. All puppies were stillborn and the dog was confirmed positive for *B. canis* on serological testing. Our patient was also found to have *B. canis*, which is a particularly rare cause of human brucellosis. She was treated with ceftriaxone, rifampin, and gentamicin before delivery and switched to doxycycline and ceftriaxone postpartum until negative. The patient was instructed not to breastfeed. After treatment, the patient felt well and the baby was healthy.

Conclusions: When evaluating patients, it is necessary to obtain a social history including animal exposures to rule in or rule out zoonotic infections such as brucellosis. It is important to establish a suspected brucellosis infection in pregnancy and begin antibiotic treatment as soon as possible to prevent maternal and fetal complications. The treatment regimen we administered was an effective strategy, particularly for pregnancy, when typical treatments are contraindicated.

Keywords: Brucellosis; pregnancy; dogs; case report

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Introduction

Brucellosis is one of the most prevalent zoonotic illnesses worldwide (1,2). Most cases occur in developing countries; human brucellosis is rare in the United States with approximately 124 cases recorded in 2023 by the Centers for Disease Control and Prevention (CDC) (3). The causative pathogens, *Brucella* spp., are small, Gram-negative coccobacilli. Of the 13 species, *B. abortus*, *B. melitensis*, *B. suis*, and *B. canis* cause human infection (4,5). *B. melitensis* is the most common cause of human brucellosis worldwide (2).

Most cases of human brucellosis occur through

^ ORCID: 0000-0002-9064-8526.

consumption of unpasteurized dairy products or contact with infected animals, their tissues, or body fluids (6,7). Other forms of transmission include inhalation of aerosols, sexual transmission, and direct contact through wounds, skin, or mucous membranes. Although extremely rare, human-to-human transmission may occur, including vertical transmission during pregnancy or through breastmilk (2,8).

Clinical manifestations of brucellosis are variable, nonspecific, and can range from asymptomatic to severe disease. Common symptoms include fever, sweats, fatigue, myalgia, arthralgia, and headache (9). Incubation period can range from 5 days up to 6 months but is often 2–4 weeks (10,11). The infection can lead to osteomyelitis, endocarditis, meningitis (5,10), and in pregnancy brucellosis, is associated with adverse obstetrical outcomes (12). We present a case of human brucellosis due to *B. canis* in a pregnant female acquired through transmission from a domestic dog, and the subsequent treatment course. We present this article in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-110/rc).

Case presentation

A 17-year-old gravida 2, parity 1 (G2P1) at 35 weeks and 2 days (35w2d) gestation presented to the hospital with 10 days of lower back pain, nausea, vomiting, and costovertebral-tenderness. She had suspected pyelonephritis. Blood and urine cultures were drawn prior to the initiation of empiric intravenous (IV) antibiotics. While admitted, the patient remained afebrile and normotensive. Blood cultures showed no growth at 48 hours; urine cultures grew urogenital flora. The patient reported resolution of symptoms and was discharged two days later on a 14-day course of cephalexin.

Three days after discharge, our microbiology laboratory identified *Brucella* spp. by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) from the patient's blood cultures at 96 hours. The patient was contacted and instructed to return to our facility for readmission. Blood cultures were sent to the Mississippi State Department of Health and subsequently the CDC for confirmation. Upon return, the patient continued to deny any systemic or focal symptoms, and her physical exam was unremarkable. The patient was started on ceftriaxone 2 g IV every 12 hours and rifampin 600 mg by mouth (PO) every 24 hours. Gentamicin 5 mg/kg IV was started a day later and these three antimicrobials were continued throughout her admission. During this time, she remained afebrile and hemodynamically stable. A transthoracic echocardiogram was negative for endocarditis. Further imaging studies for evaluation of metastatic sites of infection were deferred until after the patient delivered. Testing done by the CDC confirmed the identification of *B. canis* by polymerase chain reaction (PCR). Notably, *Brucella* immunoglobulin (Ig) IgM and IgG serologies were negative by enzyme-linked immunoassay. Upon questioning, the patient did not have any significant travel history. She denied any sick household contacts. She reported that her only non-human exposure was to her pet dog. She did report that she had assisted with her dog's delivery of a litter of stillborn puppies about 6 weeks prior to the onset of symptoms.

After 8 days, the patient was discharged on rifampin and ceftriaxone with plans to later transition to rifampin and doxycycline after she delivered. Gentamicin was given while inpatient and stopped after 7 days upon her discharge. Around 2 weeks later, the patient was readmitted for delivery. Liver function tests were noted to be elevated upon readmission with alanine aminotransaminase noted at 287 units per liter (U/L) and aspartate aminotransaminase noted at 141 U/L, so rifampin was discontinued. These labs had been normal during her previous admission. The patient delivered at 39w1d via vaginal delivery with no complications. Ceftriaxone was continued, and doxycycline 100 mg by mouth (PO) twice daily was initiated after

Highlight box

Key findings

- A 17-year-old gravida 2, parity 1 (G2P1) was admitted with suspected pyelonephritis at 35 weeks and 2 days (35w2d) gestation. Blood cultures were positive for *Brucella* spp. Upon further investigation, the patient was diagnosed with brucellosis after she assisted in the delivery of puppies.

What is known and what is new?

- Most cases of human brucellosis occur through consumption of unpasteurized dairy products or contact with infected animals, their tissues, or body fluids.
- In pregnancy, brucellosis is associated with adverse obstetrical outcomes.
- This case report is unique in highlighting brucellosis in pregnancy secondary to assistance in the delivery of puppies.

What is the implication and what should change now?

- A thorough social history workup is needed especially in pregnant patients as the potential risk of a missed diagnosis of brucellosis is potentially detrimental to both the mother and newborn.

delivery.

Additional studies, done postpartum, including computed tomography (CT) scan of the chest, abdomen, and pelvis; magnetic resonance imaging (MRI) of the spine, and transesophageal echocardiogram (TEE), revealed no metastatic foci of infection. Surgical pathology of the placenta including membrane rolls and umbilical cord with full-thickness sections observed under the microscope did not show evidence of brucellosis. Trimmed, the mature placenta weighed 560 grams. There was mild maternal decidual arteriopathy noted, but no acute chorioamnionitis was identified. Blood cultures taken from the newborn on the day of delivery showed no growth after 5 days. The patient was discharged on PO doxycycline and IV ceftriaxone, and she completed a total of 6-week-course from her first negative blood cultures. The patient was instructed not to breastfeed during antibiotic treatment.

The patient and her family initially declined to euthanize the dog when it was recommended; however, the dog later confirmed positive for *B. canis* on serological testing done by its veterinarian and was eventually euthanized. At the time of follow-up near the completion of antibiotic therapy, the patient reported that she was feeling well and that her baby was healthy. Liver function tests had normalized upon repeat testing.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report was not obtained from the patient or the relatives after all possible attempts were made.

Discussion

The first case of human abortion due to brucellosis was reported in 1905 by Thierry followed by the second case in 1906 by Devoir (12,13). While the association of brucellosis with adverse pregnancy outcomes first dates to the early 1900s, there has historically been some controversy regarding whether brucellosis is associated with an increased risk of adverse obstetric outcomes in humans (2,12-15). However, several more recent studies have found brucellosis to be associated with adverse pregnancy outcomes in humans, including spontaneous abortion, preterm delivery, intrauterine fetal demise, low birth weight, neonatal death, and congenital brucellosis (1,7,12,13,16,17). The incidence of abortion associated with brucellosis in humans does appear to be lower than in non-human animal species (13), partly due to the lack of erythritol in the human placenta (14). Erythritol, a 4-carbon sugar present in the placenta of some non-human animal species, is a known growth factor for *Brucella* spp. (2,13,16) and can promote expression of *Brucella* virulence factors (13,15,18). Furthermore, research suggests there is anti-brucellosis activity present in human amniotic fluid (2,13,16), making treatment of brucellosis in pregnancy of particular concern (13). In addition to obstetric complications, there have also been reports of transmission of the bacterium from the infected mothers to the obstetrics team during delivery as well as transmission to the infant through an infected mother's breast milk (2,13,19). While there is not an estimated time frame for the transmission period via breastmilk, reports of infection occurring several months after delivery assumed by breastfeeding have been documented (2,6,8,19-23). Additionally, there is uncertainty as to when a mother may resume breastfeeding after treatment initiation. Some research recommends stopping until the infection is eradicated while others state breastfeeding may resume 48–96 hours after treatment begins (13,21-23).

Of note, our patient was found to have *B. canis*, which is a particularly rare cause of human brucellosis. There are less than 60 human cases of *B. canis* infection reported internationally as of a 2022 report but human exposure is likely underrecognized due to lack of *B. canis* serologic tests for humans (5,10,24). *B. canis* is endemic in Asia, Africa, and the Americas (13). The incidence and prevalence of brucellosis among pregnant women are unknown even in endemic regions. A large multicenter study reported 242 (2.1%) pregnant women among 11,602 adult brucellosis patients (13). Although predominantly in dogs, there is documentation of positive antibody titers for *B. canis* in foxes and coyotes and reports of *B. canis* in cattle and cats (4,25). Transmission to humans occurs mainly through exposure to infected dogs and their fluids, particularly maternal-fetal tissue present during delivery of puppies (5). Current seroprevalence in dogs in the United States is unknown. Previous studies done in the 1970s found that seroprevalence rates in the United States range from 0–10.1% among various shelter, stray, or domestic dog populations (4). A 2018 cross-sectional study of 571 shelter dogs in Mississippi by Hubbard *et al.* estimated a mean true prevalence of *B. canis* of 7.4% (26). Infected dogs may display nonspecific symptoms, including fatigue and weight loss. Manifestations may include spondylodiscitis, epididymitis, orchitis, and prostatitis (4,10). The cure is often difficult to achieve in dogs, and persistent infection or relapse are common;

euthanasia is generally recommended (10). The CDC recommends post-exposure prophylaxis mainly to workers with high-risk exposure although considerations may be made on a case-by-case basis (27).

Although serologic testing is commonly used for diagnosis of infection with the *Brucella* genus, PCR and culture were the only options for diagnosing *B. canis* in our patient (10,24,27). This is due to the aforementioned limits on serologic testing in humans. *Brucella* spp. cell wall morphology is classified as either smooth or rough based on the structure of the O-polysaccharide subunit of the lipopolysaccharide (10). Commercially available serologic assays detect antibodies against smooth *Brucella* species only (*B. abortus*, *melitensis*, and *suis*) and will therefore not detect antibodies against *B. canis*, a smooth lipopolysaccharide, which explains our patient's negative *Brucella* serologies despite confirmation of positive cultures (4,10,26,28).

Treatment of brucellosis in humans, regardless of species, typically involves combination antibiotic therapy, monotherapy is not recommended and is associated with higher rates of failure and relapse (10,29,30). The Sixth Report of the Joint Food and Agriculture Organization and World Health Organization (WHO) Expert Committee on Brucellosis from 1986 reports that rifampin 600–900 mg daily in combination with doxycycline 200 mg daily for at least 6 weeks as the treatment of choice, with doxycycline for 6 weeks in combination with streptomycin for 3 weeks as an alternate regimen (9,10,27,31). The more recent Ioannina recommendations, created from the First International Meeting on the Treatment of Human Brucellosis, published in 2007 also recommend either doxycycline-streptomycin or doxycycline-rifampin combination therapy for 6 weeks as the treatment of choice for uncomplicated brucellosis; yet, gentamicin may be substituted for streptomycin (31). Aminoglycosides are often used for shorter durations (i.e., 5–7 days) in comparison to other medications in the regimen (31). A number of other treatment regimens have been reported such as trimethoprim-sulfamethoxazole (TMP-SMX) as part of combination therapy, and ceftriaxone and fluoroquinolone-containing regimens (8,31).

Due to the risk of adverse outcomes as well as concern for the possibility of transmission to the fetus, treatment of pregnant women is of particular importance (13). However, treatment of brucellosis in pregnancy also poses some difficulty due to the teratogenicity of commonly used medications like tetracyclines, and no randomized trials exist for the treatment of brucellosis in pregnancy (9). The WHO guidelines state that rifampin is the treatment of choice in pregnancy and note that TMP-SMX and tetracycline may be considered if rifampin is unavailable, but they do not provide specific recommendations for combination therapy in pregnancy (9,12,13,17,27). The Ioannina recommendations state that data support TMP-SMX alone or combination therapy with rifampin during pregnancy.

A combination of rifampin and TMP-SMX for 6–8 weeks has commonly been used in pregnancy, although several other regimens have been reported in the literature (2,13,27,31). In a review of a retrospective cross-sectional study of 242 pregnant women by Inan *et al.*, 11 different regimens were reported, of which ceftriaxone plus rifampin was the most common regimen, followed by TMP-SMX plus rifampin, and TMP-SMX plus ceftriaxone plus rifampin (17). There was no association between these 3 most commonly used regimens and obstetric complications. In another review of 101 cases of pregnant women with brucellosis, Vilchez *et al.* described an aminoglycoside plus rifampin as the most commonly used regimen during pregnancy followed by rifampin plus TMP-SMX (12). The authors recommended the use of aminoglycoside for 1 week plus rifampin and TMP-SMX for 6 weeks (12). Successful use of rifampin monotherapy for the treatment of brucellosis in pregnancy has also been reported but should be avoided due to the theoretical risk of relapse while on monotherapy (2,31-33).

As our patient presented during the 3rd trimester, TMP-SMX was not used given its contraindication for use during the 3rd trimester due to the risk of kernicterus (2,12,13,17). Based on a review of treatment regimens reported in the literature, we elected to initiate treatment with ceftriaxone, rifampin, and gentamicin, with plans to transition to rifampin and doxycycline after delivery (30,34). Elevated liver tests later prompted the discontinuation of rifampin, and the patient was transitioned to doxycycline and ceftriaxone after delivery. She completed the remainder of her treatment course without any adverse effects noted. Gentamicin was administered for only 7 days while admitted to the hospital. The only IV medication given outpatient was ceftriaxone, which allowed for a relatively convenient outpatient regimen without the need for frequent monitoring of antibiotic levels.

Conclusions

In conclusion, the ambiguous presentation of the disease prompts a thorough social history work up especially in

pregnant patients as the potential risk of a missed diagnosis is potentially detrimental to both the mother and newborn. Given the lack of substantial updated evidence on treatment options for brucellosis in pregnancy, we believe our treatment regimen represents a potentially useful strategy in pregnancy, particularly during the third trimester when TMP-SMX cannot be used.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-110/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report was not obtained from the patient or the relatives after all possible attempts were made.

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