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Brucellosis in pregnancy: clinical aspects and obstetric outcomes

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SUMMARY

Objective: Brucellosis is a zoonosis with high morbidity in humans. This disease has gained interest recently due to its re-emergence and potential for weaponization. Pregnant women with this disease can develop severe complications. Its association with adverse obstetric outcomes is not clearly understood. The objective of this study was to describe the obstetric outcomes of brucellosis in pregnancy.
Methods: Cases of pregnant women with active brucellosis seen at the Hospital Nacional Cayetano Heredia from 1970 to 2012 were reviewed. Diagnostic criteria were a positive agglutination test and/or positive blood/bone marrow culture. Presentation and outcomes data were collected. The Chi-square test was used for nominal variables. A p-value of <0.05 indicated significance.
Results: One hundred and one cases were included; 27.7% had a threatened abortion/preterm labor, 12.8% experienced spontaneous abortion, 13.9% preterm delivery, 8.1% fetal death, and 1.1% congenital malformations. There was one maternal death secondary to severe sepsis. After delivery, neonatal death occurred in 8.1%, low birth weight in 14.5%, and congenital brucellosis in 6.4%. The most common treatment was aminoglycosides plus rifampicin (42.2% of cases). Complication rates decreased if treatment was started within 2 weeks of presentation ($p < 0.001$).
Conclusions: This is the largest series of brucellosis in pregnancy reported in the literature. Brucella presents adverse obstetric outcomes including fetal and maternal/neonatal death. Cases with unexplained spontaneous abortion should be investigated for brucellosis. Prompt treatment is paramount to decrease the devastating outcomes.

1. Introduction

Brucellosis is a zoonosis with high morbidity in animals and humans.[1,2] It is a chronic granulomatous infection,[3] capable of affecting any organ system,[3] and may masquerade as a myriad of entities.[4] It is the most widespread zoonosis worldwide, with 500 000 new cases reported annually, and is an important cause of economic loss in many countries.[3,5] Of the known species, *Brucella melitensis* causes the majority of cases globally and has a predisposition for recurrence and chronic stages.[1]

In endemic countries, brucellosis is typically acquired through the consumption of dairy products. It affects both genders equally,[1] and special attention must be given to those with an impaired immunological status such as pregnant women, since entities such as typhoid fever, influenza, and hepatitis E have been shown to be more severe in pregnant women,[6] presenting higher mortality rates.

Brucellosis in pregnancy is associated with adverse outcomes such as spontaneous abortion, preterm delivery, chorioamnionitis, and fetal death.[7] However, it is not clear whether these outcomes are more common than in other infectious diseases.[8] The incidence of abortion is higher and prompt therapy can be life-saving for the fetus.[9]

A renewed scientific interest in brucellosis has been fuelled by its recent re-emergence and enhanced surveillance,[5] its potential to be weaponized,[10] and growing international tourism and migration. However, reports on brucellosis in pregnancy published in the literature are scarce,[9,11–13] thus studies focusing on clinical presentation, adverse obstetric outcomes, and treatment prognosis are warranted. In this scenario, the objective of the present study was to analyze the obstetric outcomes of pregnancies complicated by brucellosis. A 40-year treatment experience of brucellosis (by *B. melitensis*) in pregnancy in an endemic area is presented.

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2. Materials and methods

The Institutional Review Boards Committee of the Cayetano Heredia Peruvian University and the Cayetano Heredia National Hospital (HNCH) reviewed and approved the methodology of this study. The design of the study was a retrospective case series.

Cases with a diagnosis of brucellosis in pregnancy, including those with known brucellosis who became pregnant during the course of the disease, were selected. These cases were identified from patients seen at the HNCH, in the departments of infectious diseases and tropical medicine, and obstetrics and gynecology, and at the infectious diseases in pregnancy clinic, a private clinic of one of the authors (E.G.). Cases initially presenting to the study institution, and also those referred from other institutions (hospitals, private clinics, primary care centers) for consultation and more sub-specialized management, were included. All cases had been identified and followed prospectively for other research purposes as part of an ongoing research protocol since 1970 – the Brucellosis Study Protocol – which identifies and follows patients with brucellosis seen at the study institution.

To ensure that all cases were included, all HNCH discharge and consultation registries for the period 1970 to 2012 were reviewed, and newly identified cases were contacted by phone or home visit.

Study inclusion criteria were the following: patients with a current pregnancy or recent delivery/abortion; patients with known brucellosis who became pregnant or had a spontaneous abortion during the course of the disease; and diagnosis of brucellosis, made according to standard criteria: (1) agglutination test positive for *B. melitensis* (in plate $\geq$1:160; in tube agglutination standard (SE) $\geq$1:160, blocking antibody titer (BAB) $\geq$1:80); (2) positive culture for *B. melitensis* in blood or bone marrow. Cases with inadequate follow-up or incomplete data were excluded.

Data collection forms designed prospectively for the Brucellosis Study Protocol were reviewed: the Brucellosis Study Protocol form includes information related to demographics, risk factors, clinical presentation (signs/symptoms, duration of the disease, clinical stage, severity), and laboratory data; the Brucellosis in Pregnancy Study form includes information regarding pregnancy outcomes and treatment; the Follow-up Visit forms collect information from follow-up visits related to the resolution of symptoms, recurrence, and other treatment regimens.

The clinical stage of the disease was defined according to the duration of symptoms as acute (<8 weeks), subacute (8 weeks to 1 year), or chronic (>1 year). Recurrence was defined as a return of symptoms or new symptoms after complete treatment. Risk factors for brucellosis included a history of brucellosis, history of contact, consumption of unpasteurized dairy products, and certain occupations (healthcare provider, veterinarian, farmer, and butcher). Adverse obstetric history was defined as a history of spontaneous abortion and/or preterm delivery.

Hematological disease severity was classified as mild (episodes of bleeding such as epistaxis or microhematuria with a normal platelet count), moderate (purpuric syndrome), or severe (severe bleeding disorders such us gastrointestinal bleeding, hemoptysis with no other pulmonary disease, severe thrombocytopenia $<50 \times 10^9$ platelets/l, and disseminated intravascular coagulation). Liver disease severity was classified as mild (elevation of liver enzymes and/or bilirubin with hepatomegaly, no jaundice), moderate (jaundice with elevation of liver enzymes and/or bilirubin between 2- and 10-fold), or severe (jaundice with elevation of liver enzymes and/or bilirubin over 10-fold). Joint disease was defined as peripheral (clinical diagnosis with or without radiological confirmation) or sacroiliitis (pain in the sacroiliac joint that could be reproduced by specific joint examination maneuvers independent of radiological findings), as described previously.[14]

The severity of the disease was defined as mild (no complications or depression only), moderate (complications such as arthritis, mild/moderate liver disease, peripheral neurological involvement, psychiatric disorder, and dermatological conditions in stable condition), or severe (disseminated intravascular coagulation, severe central nervous system disease, respiratory distress syndrome, liver failure, endocarditis, and cardiac tamponade).

During pregnancy, treatment regimens included rifampicin, macrolides, aminoglycosides, and co-trimoxazole. Tetracyclines were not used. A combination of two drugs was prescribed for 4–6 weeks, with aminoglycosides for 7–10 days. After delivery/abortion, treatment regimens consisted of tetracyclines plus aminoglycosides or rifampicin. Tetracyclines were avoided during lactation, and when tetracyclines were ordered, lactation was discouraged. Macrolides were used in specific cases.

Patients were followed systematically at the HNCH infectious diseases clinic by one of the authors (E.G.), at the department of obstetrics and gynecology by obstetricians, and at the department of neonatology that was consulted during prenatal care. At delivery there was a special evaluation of the newborn by neonatologists. Upon mother and newborn discharge from the hospital, mothers were counseled regarding newborn follow-up. When a patient did not return for follow-up or delivered at another facility, attempts were made to contact the patient by phone or home visit, and information was collected.

All data were analyzed using SPSS software version 20. All frequencies were represented in percentages. The Chi-square test was used to compare nominal variables. A p-value of <0.05 with a 95% confidence interval was used to indicate statistical significance.

3. Results

A total of 133 cases were identified; 32 cases were excluded (27 due to insufficient data and five withdrew from the study). Thus, 101 cases were included for analysis (Figure 1).

3.1. Demographics

Maternal age at presentation ranged from 15 to 45 years (mean 26.1 years), with most aged between 25 and 29 years (Table 1). In 100 cases (99.1%), risk factors for brucellosis were identified; 90.8% reported the ingestion of non-pasteurized dairy products. An adverse obstetric history was associated with a chronic course of the disease ($p = 0.01$, Table 1). The trimester at presentation was available for 99 cases, and was most commonly the first trimester (Table 1).

3.2. Clinical presentation

All cases presented with clinical signs/symptoms, the most common being fever (Table 2). Most were in the acute stage ($p = 0.01$), with mild severity (Table 2).

3.3. Laboratory results and diagnostic criteria

At presentation, brucellosis was top in the differential at the first visit in 50 cases (49.5%), was suspected in 21 cases (20.8%), and was not part of the differential in 30 cases (29.7%). Blood cell count data were available for 91 cases. Anemia was found in 63 cases (69.2%), leukocytosis in 10 (11%), leukopenia in 12 (13.2%), and lymphopenia in 29 (31.9%). Thrombocytopenia developed in four out of 26 cases (15.4%). All cases had positive agglutination titers, and blood culture was positive in 33 cases (32.7%).