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ORIGINAL ARTICLE

Brucellosis in pregnancy: a 6-year clinical analysis

Mertihan Kurdoglu · Ertan Adali · Zehra Kurdoglu · Mustafa Kasim Karahocagil · Ali Kolusari · Recep Yildizhan · Zehra Kucukaydin · Hanim Guler Sahin · Mansur Kamaci · Hayrettin Akdeniz

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Abstract
Aim To review our experience with brucellosis in pregnancy and to characterize the risk factors, clinical presentations, the rates of possible perinatal complications, and the effect of hospitalization on pregnancy outcomes.
Methods We reviewed the medical records of 21 pregnant women at a tertiary care hospital and 12 at a maternity hospital, who presented with acute, subacute, chronic, or relapsing brucellosis. Their risk factors and clinical presentations were defined. The reproductive outcomes of 29 cases were compared within themselves according to the hospitals they were managed and with the outcomes for all women followed in the maternity hospital for the period from January 2008 through December 2008.
Results Consumption of unpasteurized dairy products had occurred in 92.3% of the cases. Spontaneous abortion, intrauterine fetal death, and preterm delivery rates were 24.14, 3.45, and 6.9%, respectively. Only spontaneous abortion rate substantially exceeded that among the general population of pregnant women in our maternity hospital ($P < 0.05$). Hospitalization did not affect pregnancy outcomes significantly ($P > 0.05$).
Conclusions Brucellosis in pregnancy is associated with increased incidence of spontaneous abortion without an association with the magnitude of serum agglutination titer, the clinical type of brucellosis and hospitalization. In endemic areas with habitants of low socioeconomic class and low educational level, educating women of childbearing age about brucellosis may help to prevent the disease and its complications in pregnancy.

Keywords Brucella · Brucellosis infection · Pregnancy · Abortion · Preterm labor · Intrauterine fetal demise

M. Kurdoglu · E. Adali · Z. Kurdoglu · A. Kolusari · R. Yildizhan · Z. Kucukaydin · H. G. Sahin · M. Kamaci
Department of Obstetrics and Gynecology,
Yuzuncu Yil University School of Medicine, Van, Turkey

M. K. Karahocagil · H. Akdeniz
Department of Clinical Microbiology and Infectious Diseases,
Yuzuncu Yil University School of Medicine, Van, Turkey

M. Kurdoglu (✉)
Yuzuncu Yil Universitesi Tip Fakultesi,
Kadin Hastaliklari ve Dogum Anabilim Dali, Van, Turkey
e-mail: mkurdoglu@yyu.edu.tr; mkurdoglu@doctor.com

Introduction

Brucellosis is primarily a zoonosis found in both domestic and wild animals and is transmissible to humans through direct contact with such infected animals, consumption of their infected dairy products, or inhalation of aerosols. Although aggressive public health measures have dramatically reduced the number of brucellosis cases in developed countries, the disease remains endemic in many parts of the world, especially in Latin America, Africa, Asia, and Mediterranean countries [1].

The occurrence of brucellosis during pregnancy is of special interest due to the controversy over whether the Brucella plays any unique role in human abortion or not [2]. Although it is thought that brucellosis causes fewer spontaneous abortion in humans than it does in animals due to the lack of erythritol, a preferential medium and growth factor for Brucella, in the human placenta [3] and the presence of anti-Brucella activity in human amniotic fluid [4], there is some evidence that it may cause a higher rate of complications, such as abortion, preterm labor, and intrauterine fetal demise, more frequently than do other bacterial

infections [5]. Maternal bacteremia, acute febrile reaction, toxemia, and disseminated intravascular coagulation are postulated to be the mechanisms by which brucellosis may cause spontaneous abortion and intrauterine fetal demise in pregnancy [6, 7].

Khan et al. [8] showed that antimicrobial therapy had a strong protective effect against abortion and attracted attention to the necessity of treating pregnant patients who have brucellosis immediately. Since most of the patients with brucellosis are expected to be low educated and poor, low compliance to antimicrobial therapy and inadequate duration of treatment are highly possible on an outpatient follow up. Therefore, it would be interesting to investigate whether hospitalized patients had better pregnancy outcomes or not.

In the present study, we reviewed the cases of brucellosis during pregnancy in a tertiary-care hospital together with those in a maternity and children's hospital in eastern Turkey. These hospitals had been working collaboratively in the management of these patients over a 6-year period. We aimed to characterize the risk factors, clinical presentations, and perinatal complication rates for abortion, preterm labor, and intrauterine fetal demise, and the effect of hospitalization on pregnancy outcomes.

Methods

The hospital of the Medical Faculty of Yuzuncu Yil University (Van, Turkey) has served the tertiary level medical needs of the population living in the easternmost region of Turkey since 1994. Van Maternity and Children's Hospital (Van, Turkey) has served the secondary level gynecologic and perinatal needs of the same population since 1989.

The clinical records of all pregnant patients with brucellosis, who were admitted and managed by these hospitals, were analyzed retrospectively with respect to their medical histories, and clinical and laboratory findings as well as pregnancy outcomes and complications. Twenty-one cases had been managed by Obstetrics and Gynecology Department together with the Infectious Diseases and Clinical Microbiology Department of the Hospital of the Medical Faculty of Yuzuncu Yil University, Van, Turkey, from January 2003 to September 2008. Twelve patients had been managed at Van Maternity and Children's Hospital from January 2006 to September 2008. Pregnancy outcomes of patients who were treated for brucellosis at our hospitals but lost to follow-up were not taken into consideration in the interpretation of the data regarding perinatal complications. Since one patient was in the third trimester during the study period, her data were also excluded from this part of the study. The reproductive outcomes of 29 cases were compared with the outcomes for all women followed in the maternity hospital for the period from January 2008 through December 2008.

The first trimester of pregnancy was defined as a gestational age of $\leq$12 weeks, the second trimester as >12 to $\leq$24 weeks, and the third trimester as >24 weeks. In parallel with previous similar studies [6, 8], fetal death that occurred at less than 24 weeks of gestation was considered spontaneous abortion, while fetal death that occurred after 24 weeks of gestation was designated "intrauterine fetal death". Preterm delivery was defined as the birth of a baby before 37 weeks but after 24 weeks of gestation.

Brucellosis was diagnosed by standard tube agglutination test (STA). It was performed in pregnant patients whose clinical findings resembled brucellosis. STA positivity of $\geq$1/160 or positivity in Coombs STA, or fourfold or more increase in the STA level performed 2 weeks separately, or a positive growth of Brucella species from blood and body fluids were accepted as diagnostic criteria. Brucella abortus 99S antigens of Cromatest (Lineear Chemicals, Barcelona, Spain) were used for STA. All patients underwent routine laboratory tests. Blood and other body fluid cultures were taken from patients depending on their clinical findings. Cultures were identified by automated culture identification systems, namely Bactec 9000 Diagnostic System [BD BACTEC Instrumented Blood Culture System (Franklin Lakes, NJ, USA)] up to December 2004 and after that time with Phoenix Diagnostic Systems (7 Loveton Circle Sparks, MD, USA).

Other common bacterial and protozoan causes of abortion, fetal death and preterm delivery [toxoplasmosis, rubella, cytomegalovirus (CMV) and herpes simplex virus (HSV)] were ruled out by enzyme linked immunosorbent assay technique (ELISA). From the radiologic examinations, only ultrasound (USG), magnetic resonance imaging (MRI), and echocardiography were performed when needed to investigate focal involvements.

Depending on the history, symptoms, and clinical presentation time, the patients were divided into three groups: acute (0–2 months), subacute (2–12 months), and chronic (>12 months). Those who had been diagnosed with brucellosis previously and cured appropriately but whose clinical and laboratory findings had become positive again were regarded as relapsing patients.

Antepartum antimicrobial treatment was given to all pregnant women with brucellosis. In the Hospital of the Medical Faculty of Yuzuncu Yil University, all of the patients were hospitalized in the Infectious Diseases and Clinical Microbiology Department for at least 3 weeks and managed only by two specialists. In Van Maternity and Children's Hospital, all pregnant women with brucellosis were consulted by specialists from the Infectious Diseases and Clinical Microbiology Clinic and managed by various specialists on an outpatient basis.

Socioeconomic status of the patients was defined according to their monthly incomes as low (US$ <500), medium (US$ 500–850), or high (US$ >850).

Statistical analyses were carried out using the SPSS® statistical software package (SPSS for Windows version 17.0, SPSS Inc., Chicago, Illinois, USA). The Z test or Fisher's exact Chi-square was used to compare two proportions. Chi-square test was used to determine the relationship between categorical variables. A P value of <0.05 was considered statistically significant.

Results

From 2003 through 2008, there were 342 cases of brucellosis at the Hospital of the Medical Faculty of Yuzuncu Yil University of which 21 (6.14%) occurred in pregnant women (cumulative incidence, 2.64 pregnant brucellosis cases per 1,000 deliveries). From 2006 through 2008, there were 12 cases of brucellosis during pregnancy at Van Maternity and Children's Hospital (cumulative incidence, 0.42 pregnant brucellosis cases per 1,000 deliveries).

Table 1 shows selected characteristics of pregnant patients with brucellosis. The mean maternal age was 26.79 years. Thirteen (48.15%) out of 27 women had had 3 or more previous pregnancies and 18 out of 25 women (72%) had never spontaneously aborted before. Most of the cases presented to our hospitals during the first and third trimesters (39.39 and 33.33%, respectively). All the patients were consuming Van herby cheese (a kind of cheese manufactured mainly in rural areas by villagers) and 92.3% had a history of consumption of unpasteurized dairy products. History of stockbreeding was present in 58.82% of the patients. In 63.16 and 50% of the pregnant women with brucellosis, the disease had been diagnosed previously in the same family and in the close vicinity, respectively. The majority of the patients were in the low socioeconomic class (80%) and 60% were not literate.

Table 2 details the symptoms on clinical presentation, antibody titers for Brucella of the patients, and clinical types. As seen, sweats, fatigue, joint pain, anorexia, and myalgia were the most common symptoms. Hepatomegaly was detected in one pregnant woman and splenomegaly was observed in another patient, while none of the pregnant women had lymphadenopathy on physical examination. MRI showed sacroiliitis with abscess formation in one patient and only sacroiliitis in another complaining of joint pain in the right hip region. All pregnant women with brucellosis (n = 33) had positive serum agglutination titers that ranged from 1/160 to 1/2,560 and the geometric mean titer was 1/320. However, there was no correlation between antibody titer and pregnancy outcome ($P > 0.05$).

Overall, in 7 (24.14%) out of 29 pregnant women with brucellosis (5 acute, 2 chronic), spontaneous abortions occurred during the first or second trimesters, in 1 (3.45%) intrauterine fetal death (chronic brucellosis) occurred, and in 2 (6.9%) preterm delivery (both acute) occurred in the third trimester (Table 3). Table 3 also details pregnancy outcomes of the pregnant women with brucellosis according to the hospital. First and second trimester spontaneous abortion, intrauterine fetal death, preterm delivery and term delivery rates of the pregnant women managed at the maternity and tertiary hospitals did not differ significantly ($P > 0.05$).

It may be expected that the rate of adverse perinatal outcomes may be increased in the study group given the inherent high-risk status of it with such a low socioeconomic status. Therefore, we calculated the incidence of spontaneous abortion, intrauterine fetal death and preterm delivery

Table 1 Demographic and clinical characteristics of pregnant women with brucellosis in eastern Turkey

Maternal age in years (N = 33) (mean ± SD)	26.79 ± 5.07
Age range in years (n, %)	
16–20	1 (3.03)
21–25	14 (42.42)
26–30	13 (39.39)
31–35	2 (6.06)
36–42	3 (9.1)
Gravidity (N = 27) (mean ± SD)	4.15 ± 2.78
Number of previous pregnancies (n, %)	
0	5 (18.52)
1	4 (14.81)
2	5 (18.52)
≥3	13 (48.15)
Parity (N = 26) (mean ± SD)	2.54 ± 2.42

Table 2 Clinical presentation of brucellosis in pregnant women in eastern Turkey

	n	%
Symptoms		
Sweats (n = 27)	24	88.89
Fatigue (n = 25)	24	96
Joint pain (n = 30)	29	96.67
Anorexia (n = 23)	22	95.65
Weight loss (n = 14)	7	50
Myalgia (n = 11)	8	72.73
Clinical types (n = 30)		
Acute	20	66.67
Subacute	3	10
Chronic	5	16.67
Relapsed	2	6.67

Table 3 Pregnancy outcomes of pregnant women with brucellosis in eastern Turkey according to the hospital

	Managed at maternity hospital, *n* (%)	Managed at tertiary hospital, *n* (%)
Spontaneous abortion in first trimester	1 (9.09)[a]	2 (11.11)[a]
Spontaneous abortion in second trimester	3 (27.27)[b]	1 (5.56)[c]
Intrauterine fetal death	1 (9.09)[c]	–
Preterm delivery	–	2 (11.11)[a]
Term delivery	6 (54.54)[d]	13 (72.22)[e]
Total	11 (100)	18 (100)

[a] Acute brucellosis cases

[b] Two cases of acute, 1 case of chronic brucellosis

[c] Chronic brucellosis

[d] Three cases of acute brucellosis, 1 case of chronic brucellosis, 1 case of relapsed brucellosis

[e] Eight cases of acute brucellosis, 3 cases of subacute brucellosis, 1 case of chronic brucellosis, 1 case of relapsed brucellosis

rates for all pregnant women (80% with low socioeconomic status) followed in our maternity hospital for the period from January 2008 through December 2008. The total rate of spontaneous and missed abortions during first and second trimesters combined was 7.59% (2,577 spontaneous and missed abortions among the 33,936 women who received antenatal care during this 1-year interval). This rate was significantly lower than the value (24.14%) calculated for the pregnant women with brucellosis ($P < 0.05$). Among the remaining 31,359 pregnant women who did not abort in first two trimesters, the numbers of intrauterine fetal deaths and preterm deliveries were 76 (0.24%) and 643 (2.05%), respectively. These were not significantly different from the values calculated for the study group ($P < 0.05$).

Although febrile illness did not correlate with pregnancy outcome ($P > 0.05$) it was present in 71.43% of pregnancies ending with spontaneous abortion in the first or second trimesters. Vaginal bleeding correlated highly with pregnancy outcome ($P < 0.05$) and was present in 85.71% of the pregnancies aborting in the first or second trimesters. In 57.14% of the pregnancies with brucellosis that aborted, both vaginal bleeding and febrile illness were observed in the same patient. We did not detect any correlation between clinical types and pregnancy outcomes ($P > 0.05$).

In our records, we encountered the reports of two blood cultures yielding Brucella species that were not identified to species level. The pregnancies of both patients ended in abortions. Furthermore, placentas and fetuses of the patients were not systematically studied. We encountered only one record that indicated that the placenta was sent for pathological examination, but its histological examination result could not be found. During the study period, there were no reported cases of neonates infected with Brucella.

Discussion

Our study showed that 6.14% of the Brucella cases occurred in pregnant women. This rate is much lower than the value of 17% found by Khan et al. [8] in Saudi Arabia. Cumulative incidences of pregnant brucellosis cases per 1,000 deliveries were 2.64 over a 5-year period and 0.42 over a 3-year period at our tertiary center hospital and maternity hospital, respectively. The cumulative incidence of brucellosis per 1,000 delivered discharges was 1.3 in the study by Khan et al. [8].

One striking finding in our study was that all the patients were consuming Van herby cheese. Local consumers in Van eat this cheese at almost every meal as well as between meals [9] and consumption of its fresh form made of unboiled milk was a large risk factor (92.3%) for our pregnant women. Consumption of unpasteurized dairy products was also found to be a significant risk factor for infection in the study by Sofian et al. [10]. They also showed that knowledge about the mode of brucellosis transmission by fresh cheese appeared to prevent disease transmission. Existence of another case of brucellosis in the same home (61.3%) was also observed to be a risk factor in that study [10], which is consistent with our findings showing that 63.16% of the pregnant women with brucellosis had some family members that had been diagnosed previously. We also noted that 50% of the patients knew somebody with the disease in their close vicinity. A history of stockbreeding was present in 58.82% of our study population, and in the study by Sofian et al. [10], 87.3% of the patients were keeping farm animals.

The majority of our patients were in a low socioeconomic class (80%). Similarly, 87.3% of the brucellosis patients were habitants of rural areas in the study by Sofian et al. [10]. Their study also showed that 29.3% of the patients were illiterate while 45.8% had an educational level of elementary or less. The non-literacy rate was much higher in our study population (60%), while the proportion of the patients with an elementary or less educational level was similar (40%). These finding show that poor women of childbearing age with low educational level should be educated to prevent this disease to be seen in pregnancy.

In our study, the incidence of spontaneous abortion was 24.14% in 29 pregnant women with brucellosis whose pregnancy outcomes are known within a retrospective cohort of 33 cases. Our result is similar to that of a recent study performed by Elshamy et al. [6] in Saudi Arabia reporting an incidence of 27.7% among 55 women pregnant in the first trimester with positive Brucella antibodies.

However, since they included pregnant women with antibody titers for Brucella both less than 1/160 and more than 1/160 and we included only the cases with titers equal or more than 1/160, the abortion rate of 24.14% detected in our study is much lower than the 44.11% found for the group of patients with titers more than 1/160 in the study by Elshamy et al. [6]. Sherif et al. [11] also concluded that if the titer was higher than 1/160 the incidence of abortion was 17.6% compared to 7.7% if the titer was less than 1/160. Our total abortion rate exceeded the 10% rate reported by Criscuolo and di Carlo [12] in 200 cases of *B. melitensis* infection in pregnant women and was less than that reported by Madkour et al. and Khan et al. (40% among 30 pregnant women, and 43% among 92 pregnant women with acute brucellosis, respectively) [8, 13]. Khan et al. [8] also reported that in their routine obstetrical practice over a 1-year interval the total rate of spontaneous and missed abortions during the first and second trimesters combined was 2.8% which is much lower than our finding of 7.59%.

Intrauterine fetal death is regarded as a complication of brucellosis in pregnancy. Makhseed et al. [14] diagnosed brucellosis (acute or chronic) in 10% of 51 women in which intrauterine deaths occurred, and Elshamy et al. [6] reported that intrauterine fetal death was observed in 20.58% of pregnant women with a titer of brucellosis more than 1/160. In the study by Khan et al. [8] two-third trimester intrauterine fetal deaths (2%) were reported in a cohort of 92 pregnant women with brucellosis. In our study group, intrauterine fetal death occurred in the third trimester in only one patient diagnosed in the first trimester (3.45% in 29 pregnant women with brucellosis). Khan et al. [8] also stated that in their routine obstetrical practice during a 1-year interval the rate of intrauterine fetal death in the third trimester was 0.3% which is not so different from our finding of 0.24%.

Preterm delivery is also a major concern in pregnancies complicated by brucellosis. Preterm labor was observed in 20.58% of 34 pregnant women infected by Brucella and having antibody titers more than 1/160 [6] and in 3.26% of 92 pregnant women with acute brucellosis [8]. In our study, 2 (6.9%) of 29 pregnancies were complicated by preterm delivery; in one of them brucellosis was diagnosed in the first trimester while in the other it was diagnosed in the third trimester.

We think that the number of patients with known blood culture results in our study (2 patients) was not high enough to allow an investigation of the association between maternal bacteremic status and spontaneous abortion. However, Khan et al. [8] found no association between maternal bacteremic status and spontaneous abortion and they proposed that women with active brucellosis might abort despite the absence of erythritol in the human placenta and fetus, the absence of bacteremia, and the absence of specific histological abnormalities in the placenta. The promotility effect of endotoxin on uterine smooth muscle has been implicated in the pathogenesis of abortion in brucellosis [15, 16]. We think that it may also be the reason for the high abortion rates observed in our study. Unfortunately, in most cases, Brucella cannot be cultivated and therefore a correlation of the abortion rate with a certain Brucella species cannot be drawn. Therefore, if Brucella is successfully cultivated (like in two cases of this study), then identification at the species level is highly recommended.

The study of Khan et al. [8] demonstrated a remarkably high incidence of first and second trimester spontaneous abortions among pregnant women with active brucellosis. An allergic mechanism is proposed in order to explain habitual abortus in chronic brucellosis. Desensitization as a result of recurrent bacteremia and antigen–antibody reaction may cause spasm in myometrium by causing histamine discharge [17]. However, we did not detect any correlation between clinical types of brucellosis and pregnancy outcomes. Further studies are needed to be more certain about whether clinical stage of infection is really associated with pregnancy outcome or not.

The overall pregnancy outcomes of the patients hospitalized at the tertiary level hospital and those of the pregnant women with brucellosis followed up on an outpatient basis at the maternity hospital did not differ significantly from each other. This may be due to the relatively small number of cases. We could not find any other article related to the effect of hospitalization on pregnancy outcome. Therefore, it may be interesting to see the results of randomized prospective studies with large number of cases in order to show whether outpatient management may lead to low compliance to antimicrobial therapy in such patients or not.

In summary, the results of all available studies including ours show that a high rate of spontaneous abortion is a more consistent finding rather than high rates of intrauterine fetal death and preterm delivery, in patients with brucellosis. Because the various authors used different serological methods for the confirmation of brucellosis in relatively low number of well defined cases, the anti-Brucella antibody titers cannot be compared. This might be one of the reasons why some authors find a correlation between the anti-Brucella antibody titer and the outcome of pregnancy, whereas others do not.

As a conclusion, brucellosis in pregnancy is a risk factor for spontaneous abortion. Neither the magnitude of serum agglutination titer nor the clinical type of brucellosis was associated with the occurrence of abortion. Infected women should receive prompt antimicrobial therapy when they present for medical care. Education of the people and especially of poor women of childbearing age with low educational level is advised to prevent the disease and its complications in pregnancy.

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