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Original Article

Evaluation of the relationship between human brucellosis and pregnancy loss

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Abstract

Aim: Brucellosis is a zoonotic infection caused by bacteria of the genus Brucella. The disease causes genitourinary system involvement and abortion, which is the most critical complication of the disease, in cattle. Although it is known to cause spontaneous abortion, preterm birth and intrauterine death in humans, the number of systematic studies on the subject is limited. This study compared the patients who experienced pregnancy loss and women who carried their pregnancy to term without any problems in terms of serology for brucellosis in our region which is an endemic region.

Materials and Methods: The study was conducted in the Clinic of the Department of Obstetrics and Gynecology in Gaziantep University Hospital between August 2012-June 2013. The study was conducted with 71 patients who experienced intrauterine pregnancy loss and 109 women who carried their pregnancy to term without any problems as the control group, wherein all subjects were aged between 18 and 40. These two groups were in a similar age group and had a similar gestational age.

Results: There were 4 (5,6%) subjects who were brucella-positive in the patient group and 1 (0,9%) subjects who were brucella-positive in the control group according to the serology for brucellosis. C-reactive protein, erythrocyte sedimentation rate, aspartate aminotransferase, abortus, and parity were significantly high in women who experienced pregnancy loss ($p<0.05$). The rate of living in rural areas as well as the frequency of fever, chills, shivering and lower back pain was significantly high in the patient group. When the patient group was divided into two subgroups according to the serology for brucella, patients with positive serology had a significantly higher rate of joint pain and animal contact (livestock farming) history. Although there was no significant relationship between brucella agglutination titration and pregnancy loss, the number of the brucellosis patients and agglutination titrations were higher particularly in the group of women who experienced pregnancy loss.

Conclusion: Prospective studies that will be conducted with larger patient groups are required to better reveal the relationship between pregnancy and brucellosis. Moreover, serology for brucella can be used as a screening method to provide early treatment and prevent complications associated with brucellosis during pregnancy follow-up especially in endemic region.

Keywords: Abortus; brucellosis; intrauterine fetal death; pregnancy loss

INTRODUCTION

Brucellosis is a common zoonotic disease that is caused by bacteria of the Brucella genus, i.e. gram-negative, aerobic and small coccobacilli, and may cause significant economic losses (1, 2). The disease is a significant cause of morbidity and mortality in animals, besides causing major economic losses. It is the most common zoonotic disease globally, wherein nearly more than 500,000 new brucellosis cases are reported each year (3). The disease is particularly hyperendemic in the Middle Eastern and Mediterranean basin countries, which also include Turkey (3,4).

It is not always possible to diagnose brucellosis by isolating the causative agent. Therefore, the diagnosis is generally based on serology. However, the rate of cross-reactivity may be high in serologic tests and sensitivity can be low especially in the early phase of the disease (5).

The active microorganism can be transmitted through direct contact with infected animal materials or by consuming dairy products obtained from such animals (6). Brucellosis leads to a granulomatous inflammatory reaction that tends to become chronic in humans and may cause multiple organ involvement (7,8). Therefore, it can be confused with many diseases that cause multisystem involvement (8).

The most important complication is abortion in the presence of brucellosis, especially when the genitourinary system is affected in pregnant cattle (1). It is known to

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cause spontaneous abortion, preterm birth and intrauterine death in humans and even sequela development in the newborn in some pregnancies that were left untreated. However, there are only few studies on this subject that are conducted with large patient series, especially in Turkey (9-12).

In this study, we compared the clinical, laboratory and serologic brucellosis findings between women who experienced pregnancy loss and women who carried their pregnancy to term without any problems to investigate whether brucellosis had any effects on pregnancy loss.

MATERIALS and METHODS

This study investigated women aged between 18-40 who experienced spontaneous abortion, missed abortion and intrauterine death without a known cause and who were admitted to the Obstetrics and Gynecology Clinic of Gaziantep University between 1 July 2012 and 30 June 2013. Healthy pregnant women who were at a similar age and gestational age as the women in the patient group and who presented to the Obstetrics and Gynecology Clinic of Gaziantep University within the same period for routine follow-up were included in the control group. Patients who had obstetric problems and/or fetal problems during follow-up were excluded from the control group. Age, place of residence, history of visits to rural areas, raw milk and dairy consumption (especially cheese made of raw milk), involvement with animals, duration of complaints, presenting complaints, presence of fever, examination and laboratory findings, and other known diseases in terms of diagnosis and treatments were evaluated and recorded for all patients.

This study was planned as a prospective observational study. The cohort of the study consisted of women aged between 18-40 who experienced spontaneous abortion, missed abortion and intrauterine death without a known cause and who were followed up after admission to the Obstetrics and Gynecology Clinic of Gaziantep University Medical Faculty between July 1, 2012, and June 30, 2013. Healthy pregnant women who were at a similar age and gestational age as the women in the patient group and who presented to the Obstetrics and Gynecology Clinic of Gaziantep University Medical Faculty within the same period for routine follow-up were included in the control group.

After obtaining a detailed medical history and conducting physical examinations, complete blood count, liver function tests [ALT, AST, ALP, GGT, total bilirubin, direct bilirubin, albumin, INR (international normalized ratio)], FBG (fasting blood glucose), total cholesterol, triglyceride, urea, creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), HBsAg, Anti-HBs, Anti-HCV, Anti-HIV, Anti Toxo IgM/IgG, CMV IgM/IgG, Herpes Simplex Virus Type 1 IgM/IgG, Herpes Simplex Virus Type 2 IgM/IgG, Rubella IgM/IgG, EBV IgM, EBV IgG tests, Brucella standard tube agglutination test (STA) and Brucella agglutination test with blocking antibodies (Brucellacapt®) were performed. To exclude an autoimmune diseases that can cause pregnancy loss we tested all individuals with pregnancy loss history for auto-immunity panel [ANA (antinuclear antibody), Anti-dsDNA (double stranded antibody), RF (rheumatoid factor), lupus anticoagulants, Anti-cardiolipin IgM/G, Beta2-glycoprotein IgM and IgG].

Patients who had Brucellacapt® > 1/320 and/or STA > 1/160 were considered to be Brucella-positive according to the serology.

Inclusion and Exclusion Criteria

For patients who experienced pregnancy loss due to a known cause were excluded from the study (positive auto-immunity panel markers and viral markers). Patients who had positive results (that would indicate an acute or chronic disease) in serologic tests other than serology for Brucellosis were not included in the study.

For the control group, pregnant women who presented to the outpatient clinic but had an underlying disease or a condition that could cause pregnancy loss detected in screenings (trisomy, urinary tract infection, EBV IgM, CMV IgM, rubella IgM, HSV IgM, and positive viral hepatitis markers) were excluded from the study.

The statistics software package SPSS 17.0 for Windows was used for statistical analysis. In comparing independent groups, the T-test was used when numerical variables were normally distributed and the Mann Whitney U test was used when numerical variables were not normally distributed. $P<0.05$ was considered statistically significant.

The approval with the decision no /04.09.2012/325 dated 04.09.2012 was obtained from Gaziantep University Clinical Trials Ethics Committee for the study "Evaluation of the Relationship Between Brucellosis and Pregnancy Loss in Humans".

RESULTS

The study was conducted with 71 subjects who experienced intrauterine pregnancy loss as the patient group and 109 women who completed their pregnancy without any problems as the control group. These two groups were in a similar age group (P=0.844) and had a similar gestational age (P=0.079). Gravidity values were similar in both groups, whereas parity was higher in healthy pregnant women and abortus was higher in the patient group. Table 1 shows the mean gravidity, parity, abortus and laboratory values of the subjects included in the study. While ESR values were similar in both groups (23.46 vs. 20.22 P=0.036), CRP values were higher in the patient group (16.7 vs. 7.04 P < 0.001).

Table 2 shows the rate of brucella-positivity according to serologic tests, the demographic characteristics, and complaints of the subjects in the patient and control groups. There was no significant difference between the two groups in terms of demographic characteristics, whereas the rate of complaints (fever, chills-shivering, lower back pain) was significantly higher in the patient group. Using a cut-off value of 1/160 for STA and/or 1/320 for immunocapture, the seropositivity rate was 5.6% in the patient group and 0.9% in the control group, wherein the difference was not statistically significant (Table 2).

Table 1. Patients properties and laboratory results

	Pregnancy loss group (n=71)	Healty Pregnants (n=109)	P Value
Age	28.37 (±6.64)	28.55 (±5.77)	**0.844**
Gestation Age	18.51 (±8.78)	20.93 (±9.11)	0.079
Number of Gravity	3.25 (±1.57)	3.22 (±1.89)	0.982
Parity Number	1.21 (±1.12)	1.70 (±1.59)	**0.026**
Abortion Number	1.14 (±1.41)	0.53 (±0.91)	**0.001**
White blood cell,×10³/µL	9.787 (±3207)	11.996 (±12.784)	0.156
Haemoglobine, g/dl	12.57 (±2.12)	12.07(±0.95)	**0.033**
Hematocrit, (%)	36.59 (±7.07)	36.40 (±5.83)	0.849
Platelets, ×10³/µL	225.391 (±79039)	225.899 (±50.205)	0.958
FBG, mg/dl	101.15 (±30.42)	87.66 (±19.97)	**<0.001**
Creatinina, mg/dl	1.23 (±5.51)	0.51 (±0.12)	0.173
ALT, U/L	19.43 (±13.23)	19.39 (±8.17)	0.981
AST, U/L	25.58(±14.98)	20.42 (±7.61)	**0.003**
Total bilirubin, mg/dl	0.35 (±0.20)	0.31 (±0.27)	0.294
Albumin, g/dl	3.86 (±0.51)	3.87 (±0.48)	0.801
ESR, mm/h	23.46 (±12.72)	20.22 (±7.83)	**0.036**
CRP, mg/L	16.70 (±27.81)	7.04 (±4.42)	**<0.001**

Table 2. Brucella serology positivity rates, demographic characteristics and complaints of patient and control groups

Patient Characteristics	Pregnancy loss group (n=71)	Healty Pregnants (n=109)	P Value
Location			
Countryside	29 (40.8%)	19 (17.4%)	**0.01**
Center	42 (59.2%)	90 (82.6%)	
Occupation			
Unemployed	64 (90.1%)	86 (78.9%)	0.065
History			
Raw dairy consumption	44 (62%)	61 (55%)	0.440
Livestock farming	13 (18.3%)	14(12.8%)	0.394
Complaints			
Fever	19 (26.8%)	9 (8.3%)	**0.01**
Cold tremor	23 (46.5%)	27 (24.8%)	**0.03**
Backache	45 (63.4%)	22 (20.8%)	**<0.001**
Arthralgia	22 (31%)	32 (29.4%)	**0.870**
Brucella serology positivity	4 (5.6%)	1 (0.9%)	0.394

Table 3. Characteristics of Brucella serology positive patients

	Order	Age	Previous Pregnancy Losses	STA	Immuno-capture Aggl. Test
Patient					
	1	20	3	1/160	1/640
	2	38	3	1/80	1/320
	3	25	0	1/40	1/640
	4	22	3	1/160	1/320
Control					
	1	34	0	1/160	1/320

Aggl: Agglutination

Table 3 shows the age, number of previous pregnancy losses and titrations at which agglutination was positive in these patients.

Women in the patient group were divided into two subgroups, i.e. women with serology-positive and serology-negative results, and re-evaluated in terms of laboratory findings, patient characteristics, symptoms, and complaints (Table 4). The rates of chills-shivering and raw cheese consumption were higher in all women who experienced pregnancy loss and the rates of arthralgia and livestock farming/animal contact were higher in patients who were seropositive.Many parameters that exhibited significant differences in Table 1 did not exhibit any significant difference in Table 4.

Table 4. Comparison of the cases in the patient group according to brucella serology

	Brucella Positive (n=4)	Brucella Negatif (n=67)	P Value
Cold tremor	2 (50%)	31 (46.3%)	1.000
Fever	3 (75%)	16 (26%)	0.056
Backache	4 (100%)	41 (61%)	0.289
Arthralgia	4 (100%)	18 (26.9%)	0.008
Raw dairy consumption	2 (50%)	42 (62.7%)	1.000
Livestock farming	3 (75%)	10 (14.9%)	0.018
Age	26.26 (±6.45)	28.49 (±5.62)	0.516
Gestation Age	13.27 (±2.21)	18.82 (±8.94)	0.426
Gravity number	3.5 (±1.23)	3.24 (±1.5)	0.750
Parity number	0.5 (±1.34)	1.25 (±0.83)	0.193
Abortion number	2.25 (±1.21)	1.07 (±1.12)	0.108
White blood cell, ×10³/µL	10025 (±3420)	9772.8 (±2707)	0.880
ESR, mm/h	18.5 (±7.6)	23.76 (±17.8)	0.426
CRP, mg/L	11.16 (±16.4)	17.03 (±18.6)	0.685

STA: Standart Tube Aglutination; ESR: Eritrocyte Sedimentation Rate; CRP: C-Reactive Protein

DISCUSSION

Brucellosis is one of the most common zoonotic infections caused by bacteria of the genus Brucella (13). The incubation period of brucellosis ranges from 2-3 weeks to 6 months (14,15). Due to the long and varying incubation period, a wide spectrum of clinical symptoms and the fact that the rate of growth of this microorganism in culture is low, only 10-15% of the patients can be diagnosed. Although brucellosis is a notifiable zoonosis, it is known that the actual number of patients is higher than reported (3,16). In the first systematic epidemiologic study by Cetin et al. (17) conducted on brucellosis with 70,009 subjects in Turkey, the rate of Brucella seropositivity was reported to be 6% in the high-risk population and 1.8% in the entire study group. The same rate was as high as 27.2% in the Eastern and Southeastern cities of Turkey (18). The reported incidence of brucellosis in pregnant women ranges between 1.3-12.2% in various studies (11,19).

It is very well known that many Brucella species cause pregnancy loss in farm animals, and there are studies asserting that Brucella also causes pregnancy loss in humans (20,21). The reason why the rate of pregnancy loss due to brucellosis is lower in humans than animals is thought to be the absence of erythritol in the human placenta (22,23). There are many publications in the literature concerning the negative effects (pregnancy loss, preterm birth, congenital infection) of various microorganisms including chlamydia, *Coxiella burnetii, Listeria monocytogenes, Waddlia chondrophila, Campylobacter jejuni* and *Salmonella spp*. on pregnancy (24-27). However, it is not possible to compare the individual effects of these infections on pregnancy due to the challenges in determining the relationship of other bacteria with pregnancy loss and in calculating the incidence of pregnancy loss due to other bacteria. In this study, we included patients in whom we could serologically eliminate rubella, CMV, EBV and toxoplasma infections. Bacteremia, acute febrile reaction, toxemia and/or DIC are the main mechanisms that cause pregnancy loss in all bacterial infections (11,28). Contractile effect of endotoxins on uterine smooth muscle cells is thought to be the main cause of the pregnancy-related complications of brucellosis (29). In a study by Khan et al. conducted with 545 brucellosis cases between 1983 and 1985, 17% of the patients were pregnant (92/545) and 43% of these patients were reported to have pregnancy loss (19). The rate of pregnancy loss in pregnant women diagnosed with brucellosis is 10-44% according to previous studies (10,11,19,30,31). Contrary to the literature, Buzğan et al. conducted a study in Van with 1028 patients diagnosed with brucellosis and reported that all pregnant women (1.7%) carried their pregnancy to term without any problems (32).

In another seroprevalence study published in Jordan that consisted of 890 subjects, i.e. 445 women who experienced pregnancy loss and 445 control subjects (women who carried their pregnancy to term without any problems), rate of Brucella seropositivity was 1.8% in the study group and 1.0% in the control group, wherein the difference was not statistically significant (33). In the said study, Abo-Shehada et al. accepted the presence of agglutination at any titration as "Positive" for Rose Bengal and/or Brucella standard tube agglutination. Similarly, accepting the presence of agglutination at any titration as positive in our study, the positivity rates were 14.1% in the study group and 4.6% in the control group, wherein the difference was statistically significant (P = 0.028). However, the same values were 5.6% and 0.9%, respectively, when the cut-off value for immunocapture was 1/320, wherein the difference was not statistically significant. In a study by Khan et al. (19), pregnant women who were diagnosed with brucellosis were divided into two groups, i.e. those above and below 1/2560 titration, and it was found that there was no relationship between titration and pregnancy loss or preterm birth. No relationship has been observed between pregnancy loss and titration levels in many previous studies (10,19,28). However, it is not possible to compare these studies due to the differences between the employed methods.

It was shown that the pregnancy complications associated with Brucellosis were especially observed within the first 2 trimesters, wherein Khan et al. (19) also reported that the rate of pregnancy loss was 43% within the first two trimesters and 2% in the third trimester. In this study and most of the similar studies, patients were only diagnosed serologically without making any acute-chronic distinction. A patient diagnosed in the third trimester generally has chronic brucellosis. Consequently, it is more accurate to say that the risk of pregnancy loss due to brucellosis gradually decreases throughout the gestational weeks, rather than saying that brucellosis more frequently causes pregnancy loss in the first two trimesters than the third trimester. A patient who got infected in the third trimester and a patient who got infected in the first trimester may have similar risks. There is a need for further studies on this subject that are conducted with larger patient groups and that involve more detailed medical history and laboratory tests. In our study, patients who were brucella-seropositive and who experienced pregnancy loss were at gestational week 13.80 (± 3.64), which was supportive of the literature. It was found that the pregnancy loss in these patients was observed earlier than the patients who were brucella-seronegative, which implies that brucellosis more specifically causes early pregnancy loss.

As shown in Table 1, the number of previous abortions was significantly higher in the patient group (P = 0.001). This may have two reasons. First, patients may have had pregnancy loss due to other rheumatic and/or immunologic causes that we couldn't show with our assays. Although there was no information that would explain such a condition according to the medical histories of our patients, known causes of pregnancy loss were not eliminated by laboratory tests in our study. Second, if the patient has chronic brucellosis, it may be the cause of recurrent abortion, and there are studies that support such a possibility in the literature (34). The fact that there were no significant differences between brucella-seropositive and brucella-seronegative patients increased the possibility that mechanisms other than brucellosis were involved.

According to a study by Buzgan et al. (32) conducted with 1,028 brucellosis patients, ESR (51.3%) and CRP (58.4%) levels were significantly high according to the laboratory findings, which were similar to the results of our study. Our study also showed that inflammatory marker levels (ESR, CRP) were significantly higher in the patient group than the control groupand also the difference between seropositive vs negative patient group is significant p=0,036 vs p<0,001. Like many studies in the literature which showed high inflammatory marker levels in brucellosis patients (32,35). Regardless of brucella serology, the fact that these markers were high in the entire patient population implied that the mentioned high level could due to the physiopathological changes that occurred during pregnancy loss. In some studies, it was reported that anemia and elevated CRP levels were observed in acute and subacute forms of brucellosis, elevated ESR and lymphomonocytosis in all forms of brucellosis and rheumatoid factor positivity in chronic and relapsed brucellosis patients (6,36).

In terms of patient complaints, lower back pain and joint pain were significantly more frequent. However, it was remarkable that these complaints were also frequent in the control group. This is probably because of the mechanical effect of pregnancy. Fever and cold-tremorwere also significantly frequent, wherein it was reported in some publications that the symptoms were rather associated with the stage of the disease. In another study, fever, joint pain, and lower back pain were found to be particularly associated with acute disease, and depression symptoms were found to be rather associated with chronic disease (37,38).

CONCLUSION

One of the limitations of our study was that it did not contain treatment and follow-up data of the patients after they were diagnosed. Khan et al. (16) showed in their study that antibiotherapy was protective against pregnancy loss. According to a study by Roushan et al. (28), 10 (53%) of the 19 patients who were diagnosed with brucellosis experienced abortion. Another observation made in the same study was that the patients could carry their pregnancies to term if they could be treated before they had vaginal bleeding. In addition, it was shown in many studies that providing early treatment protected both the mother and the baby (10). On the other hand, it was shown that the treatment could not prevent pregnancy loss in patients who presented to the hospital after vaginal bleeding had started (19). In fact, this finding has also shown that the most important thing in pregnancies with

brucellosis is the provision of early diagnosis as well as early and rapid treatment. Otherwise, the administered treatment cannot provide the continuity of pregnancy. As is seen, it is of utmost importance to provide early diagnosis and start the treatment rapidly in pregnancies with brucellosis. Therefore, even if they are asymptomatic, it may be necessary to evaluate brucellosis serology during pregnancy follow-up, especially in endemic regions. Studies on this subject were generally designed as a retrospective and/or only serology-based studies due to the microbiological and social challenges, which makes it difficult to access certain data such as stage and duration of the disease, gestational age, pregnancy loss risk ratio, and risk factors. There is a need for further studies conducted with larger patient groups that include more detailed medical histories and laboratory data.

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