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ORIGINAL ARTICLE

Brucellosis in pregnancy: results of multicenter ID-IRI study

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Abstract
Brucellosis in pregnant women is reported to be associated with obstetric complications (OCs), and adequate data for human brucellosis during pregnancy are largely lacking. We performed this multicenter retrospective cross-sectional study to evaluate the epidemiology, clinical course, treatment responses, and outcomes of brucellosis among pregnant women. The study period comprised a 14-year period from January 2002 to December 2015. All consecutive pregnant women diagnosed with brucellosis in 23 participating hospitals were included. Epidemiological, clinical, laboratory, therapeutic, and outcome data along with the assessment data of the neonate were collected using a standardized questionnaire. Data of 242 patients were analyzed. The OC rate was 14.0% (34/242) in the cohort. Of the 242 women, 219 (90.5%) delivered at term, 3 (1.2%) had preterm delivery, 15 (6.2%) aborted, and 5 (2.1%) had intrauterine fetal demise. Seventeen (7.0%) of the newborns were considered as low birth weight. Spontaneous abortion (6.1%) was the commonest complication. There were no maternal or neonatal deaths and pertinent sequelae or complications were not detected in the newborns. Splenomegaly ($p = 0.019$), nausea and/or vomiting ($p < 0.001$), vaginal bleeding ($p < 0.001$), anemia (blood hemoglobin < 11 g/dL; $p < 0.001$), high level of serum aspartate aminotransferase (> 41 IU/L; $p = 0.025$), oligohydramnios on ultrasonography ($p = 0.0002$), history of taking medication other than *Brucella* treatment during pregnancy ($p = 0.027$), and *Brucella* bacteremia ($p = 0.029$) were the significant factors associated with OCs. We recommend that pregnant women with OC or with fever should be investigated for brucellosis if they live in or have traveled to an endemic area.

Keywords Pregnancy · Brucellosis · Obstetrics · Abortus · Intrauterine fetal demise · Risk factors

Introduction

Brucellosis, one of the zoonotic infections caused by *Brucella* spp., is a major health problem. The disease is found worldwide and is especially seen in South and Central America, India, the Mediterranean basin, the Balkans, and the Middle East [1]. Brucellosis is still endemic in Turkey with an incidence of 25.7 cases per 100,000 population [2]. Although it is under control in most developed countries, the epidemiology of brucellosis has changed significantly in the last years with the emergence of new outbreaks in the Balkan Peninsula and in some of the Asian countries, which indicates the difficulty in eradicating this infection. The disease has the potential to affect many organs of the body and results in significant morbidity [3–8].

Brucellosis during human pregnancy is reported to be associated with abortion, premature delivery, intrauterine fetal demise (IFD), and congenital brucellosis with malformations, neonatal death, and low birth weight (LBW) [9–13]. Although its role in causing abortion in animals is well-documented, adequate data regarding obstetric complications (OCs) in human pregnancies are largely lacking. For this reason, we performed this multicenter study to detail OCs in pregnant women with brucellosis.

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Materials and methods

Study design and patients

This multicenter retrospective cross-sectional cohort over a 14-year period from January 2002 to December 2015 included all consecutive pregnant women diagnosed with brucellosis in 23 participant hospitals, which were the collaborating centers of the global clinical research platform, Infectious Diseases International Research Initiative (ID-IRI). Ethical approval was obtained from the Ethics Committee of the Fatih Sultan Mehmet Training and Research Hospital's Review Board, Istanbul. Patient information was anonymized and de-identified prior to analysis.

Patient inclusion and data collection

Pregnant women with brucellosis and with/without recent delivery/abortion/IFD and women with known brucellosis who became pregnant and with/without recent delivery/abortion/IFD were the inclusion criteria. Adult males and non-pregnant women with brucellosis and pediatric brucellosis cases were excluded. All epidemiological, obstetric, clinical, laboratory, therapeutic, and outcome data along with the neonate assessment data were collected using a standardized questionnaire.

Laboratory investigations

In all patients, complete blood counts (CBCs), urinalyses, serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and blood biochemistry tests were collected. Blood specimens were cultured for 14 days and isolates were identified by automated culture systems in different centers, mainly by the BACTEC 9240 and Phoenix Diagnostic Systems (Becton-Dickinson, MD, USA). Clinical specimens other than blood were inoculated onto sheep blood and chocolate agars. All clinical isolates were defined by standard microbiological techniques such as motility, oxidase, catalase, glucose fermentation, and production of H_2S and urease. The *Brucella* immunoglobulin (Ig)M and IgG antibody ELISA test kits (Vircell™, Granada, Spain) were also used in some participant centers for diagnostic purposes. Two different commercially available *Brucella abortus* S99 antigens (Pendik Animal Diseases Research Institute, Istanbul, Turkey and Cromatest™, Linear Chemicals, Barcelona, Spain) were used. The Rose Bengal test (RBT) (Pendik Animal Diseases Research Institute, Istanbul, Turkey) and Coombs-STA test were also used for serological analysis. Depending on the symptoms and signs, the women were also evaluated for the presence of other foci of brucellosis. Abdominal ultrasonography (USG), magnetic resonance imaging (MRI), and echocardiography were performed to determine focal involvements.

Diagnosis of brucellosis The diagnosis in accordance with compatible clinical findings for brucellosis in a pregnant woman was made through laboratory confirmation. Microbiological diagnosis included a positive standard tube agglutination (STA) test or RBT and/or isolation of *Brucellae* from blood and/or human placenta and aborted fetus. The STA positivity of $\geq$ 1:160 or positivity in Coombs STA or at least a fourfold increase in the STA level performed 2 weeks apart was accepted as diagnostic criteria.

Classification of brucellosis Patients were subclassified into acute, subacute, and chronic stages according to the duration of the symptoms of disease as less than 8 weeks, 8 to 52 weeks, and more than 52 weeks, respectively.

Definitions

a) Relapse: Reappearance of clinical signs and symptoms of brucellosis after successful therapy and a positive culture or a rise in antibody titer in the absence of exposure to *Brucellae* were defined as relapse.
b) Obstetrical definitions: The first trimester of pregnancy was defined as a gestational age of $\leq$ 12 weeks, the second trimester as 13 through 24 weeks, and the third trimester as $\geq$ 25 weeks. Fetal death occurred < 24 weeks of gestation was defined as *spontaneous abortion*. Fetal death occurring at > 24 weeks of gestation was defined as IFD. Rupture of membranes prior to the onset of labor at < 37 weeks of gestation was defined as *premature rupture of membranes* (PROM). Birth through 25 to 37 weeks of gestation was defined as *preterm delivery*. Infant weight of < 2500 g at full-term birth was defined as *low birth weight* (LBW) [10].
c) Obstetric complications: The presence of at least one of the following was defined as OC: Threatened abortion, spontaneous abortion, PROM, IFD, preterm delivery, any complications or abnormalities in the newborn and infant, or maternal death after delivery of a pregnant woman with brucellosis. Otherwise, women with brucellosis were considered to have a favorable obstetric outcome.

Treatment issues, patient follow-up, and outcomes

All pregnant women included in this study were evaluated on admission and daily during their hospitalization. After establishment of diagnosis of brucellosis, antepartum antimicrobial treatment with various combinations of antibiotics including ceftriaxone and gentamicin parenterally and trimethoprim/sulfamethoxazole (SXT) and rifampicin orally was given in the appropriate doses and durations [1]. Doxycycline was not used either during pregnancy or in the lactation period. Because of risk of kernicterus in the

newborn, SXT was not used in the third trimester. After abortion or IFD, treatment regimens included doxycycline. Combined antibiotics were continued for a minimum of 6 to 8 weeks; otherwise, treatment was continued until the resolution of other foci (if any) of brucellosis. Pregnant women were followed-up during the pregnancy, the neonatal period, and after completing therapy. Cure, drug modifications, relapse, OCs, delivery outcome, neonatal and maternal status, neonatal baby birth weight, breastfeeding after delivery, and brucellosis relapses (if any) were all recorded for each patient.

Statistical analysis

The data analysis was performed by the SPSS for Windows v.16.5 (SPSS Inc., Chicago, IL, USA) software package. Patients were classified into two groups: those with adverse obstetric outcome and those with favorable obstetric outcome. Proportion comparisons for categorical variables were performed by Fisher's exact test or, where required, by the Freeman–Halton extension of the Fisher's exact test for two rows by three-column contingency table. Significance was inferred at 0.05 levels, and it was always two sided.

Results

Two hundred and forty-two pregnant women with brucellosis were included. The mean ± standard deviation (range) of maternal age was 28.8 ± 6.28 (17–50) years.

Epidemiological and obstetric history

During the 14-year study period, 11,602 adult brucellosis patients were treated and the total number of deliveries was 732,673 at the participant hospitals. The ratio of pregnancy among the adult brucellosis patients was 2.1% (242/11,602). Cumulative incidence was calculated as 3.3 brucellosis cases in pregnancy per 1000 delivered obstetrical discharges. Sixty out of 242 (24.8%) patients presented to the participant centers during the first trimester of pregnancy, 95 (39.3%) in the second, and 78 (32.2%) of them presented in the third trimester of pregnancy. Sixty-two (25.6%) of 242 women were primigravid, and 105 (43.4%) had three or more prior pregnancies (min 1, max 7). Obstetric history at prior gestations is presented in Fig. 1.

Clinical data

The descriptive clinical characteristics of women are presented in Table 1. Overall 230 (95.0%) patients were classified as having acute brucellosis. The most frequent symptoms and signs were weakness (95.4%), night sweats (89.6%), arthralgia (88.8%), and fever (83.7%). The obstetric symptoms and signs were vaginal bleeding in 22 (9.1%) and groin pain in 8 of 34 (23.5%). Coexistence of other foci of brucellosis was observed in 113 (45.9%). No systemic and uterine comorbid diseases were found in this cohort. The median (IQR) time from the onset of disease symptoms to diagnosis was 14 (10–21) days.

Microbiological and serological investigations

Blood cultures were obtained from 134 cases yielding a *Brucella* spp. in 56 (41.8%). Among the isolates subtyped, *Brucella melitensis* was identified in 36 (64.2%). A culture of two placental specimens yielded *B. melitensis*. The RBT was positive in 99.1% (223/225), and STA was positive 97.0% (225/232) with the dilution ranging from 1:160 to 1:1280. Coombs-STA was positive in all (7/7) patients with a negative STA test with dilutions between 1:160 and 1:640 (Table 2). Ten women were diagnosed with brucellosis only by positive blood cultures.

Results of women with OCs

Threatened abortion ($n = 10$), spontaneous abortion ($n = 2$) and preterm delivery ($n = 1$) on first examination, and spontaneous abortion ($n = 13$), IFD ($n = 5$) and preterm delivery ($n = 3$) in the follow-up period occurred in a total of 34 out of 242 pregnant women (14.0%) who were classified in the adverse obstetric outcome group. The remaining 208 (86.0%) women were classified in the favorable obstetric outcome group.

Obstetric USG findings

The obstetric USG was performed in 230 women and the results were as follows: Undetectable fetal heartbeat ($n = 6$), small for gestational age ($n = 12$), incomplete abortion ($n = 3$), placenta previa ($n = 6$), oligohydramnios ($n = 6$), and twin pregnancy ($n = 1$) (data not shown).

Therapeutic concerns

Following the diagnosis of brucellosis, the initial antibiotics were as follows: ceftriaxone plus rifampicin ($n = 92$), SXT plus rifampicin ($n = 79$), SXT plus ceftriaxone plus rifampicin ($n = 47$), SXT plus gentamicin/streptomycin ($n = 6$), ceftriaxone plus SXT ($n = 3$), rifampicin plus doxycycline ($n = 3$), rifampicin plus SXT plus gentamicin ($n = 3$), rifampicin plus gentamicin ($n = 1$), rifampicin plus doxycycline plus gentamicin ($n = 1$), ceftriaxone alone ($n = 5$), and cefotaxime alone ($n = 2$). Overall, empirical antibiotics were modified in 12 (4.9%) patients. The

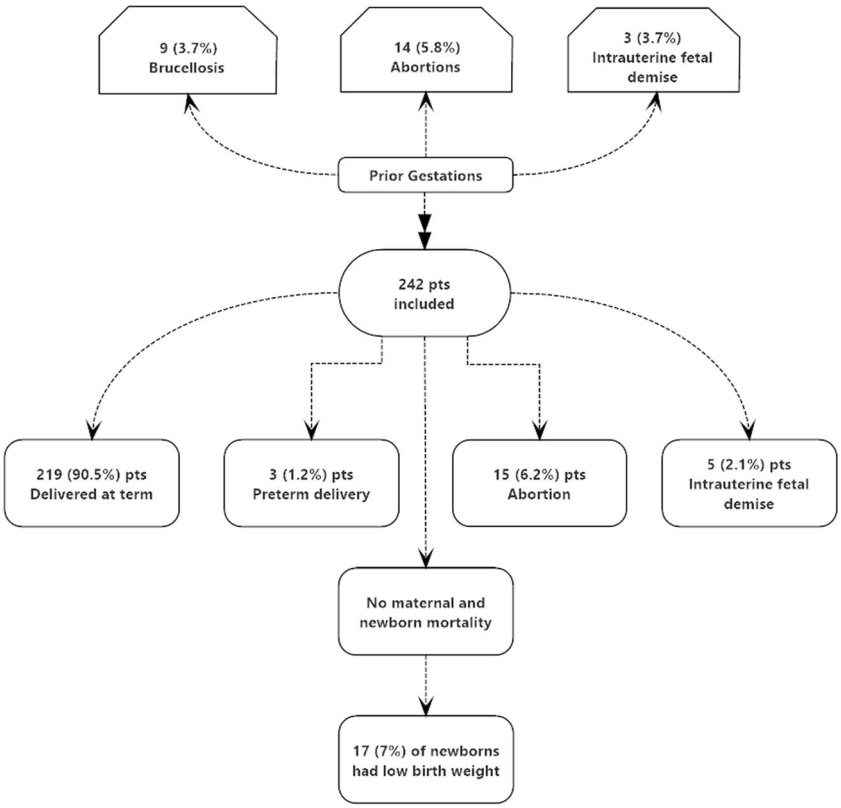

Fig. 1 Maternal and fetal outcomes in 242 pregnant women with brucellosis

median (IQR) duration of initiation of antibiotic treatment after the onset of symptoms was 15 (10–21) days.

Outcomes

The mean time until abortions according to gestational age was 13.8 ± 6.1 (6–23) weeks, and the mean time of abortions after the initiation of brucellosis therapy was 18.6 ± 20.8 (1–65) days (data not shown).

The course of the delivery is shown in Fig. 1. No maternal and newborn mortality or pertinent sequelae were detected in the newborns. Relapse occurred in a woman in the adverse obstetric outcome group 11 months after stopping doxycycline plus rifampicin therapy.

Potential risks for obstetrical complications

Splenomegaly ($p = 0.019$), nausea and/or vomiting ($p < 0.0001$), vaginal bleeding ($p < 0.0001$), anemia ($p < 0.001$), high levels of serum aspartate aminotransferase ($p = 0.025$), oligohydramnios on USG ($p = 0.002$), and any medicinal drug use (mostly an antibiotic) during pregnancy ($p = 0.027$) were significantly associated with OCs. *Brucella* bacteremia was also found to be significantly associated with OCs (12/17 (70.5%) vs. 44/117 (37.6%); $p = 0.016$) (Table 3).

Discussion

Brucellosis in pregnancy has frequently been described since initial recognition of the disease [14]. According to our data, the incidence of pregnancy in the adulthood brucellosis (2.1%) is consistent with the reported incidence rates (1.3–12.2%) for *Brucella* endemic areas in the medical literature [12, 15–17]. Basically, brucellosis in pregnant women carries the risk of trans-placental transmission that may result in preterm deliveries, IFD, and spontaneous abortions, likely to be fewer than animals [9]. Brucellosis is believed to be a significant contributor to human abortions in many developing countries [15–18]. In this study, we have found that 14% of pregnant women with brucellosis had an OC including 6.2% abortion and 2.1% IFD, which is lower than in earlier reports [15, 16, 19]. A recent retrospective study from Peru found a higher OC rate (41.8%) among the 86 patients with 11% neonatal and 1% maternal deaths [11]. We found only 8.3% of fetal loss and no neonatal and maternal mortality in this study. Congenital malformations including heart defects have been reported in newborns after delivery [13, 15]. A lower OC rate and the absence of maternal and fetal mortality in the entire study may be attributed to early diagnosis and treatment of brucellosis in Turkey. In this study, the acute form was more frequent (95%), and the symptoms during this phase, such as fever, were more helpful in establishing

Table 1 Clinical findings on admission of 242 pregnant women with brucellosis

Variable	Results
Brucellosis classification	
• Acute	230 (95.0)
• Subacute	7 (2.9)
• Chronic	5 (2.1)
Systemic symptom and signs	
• Weakness	231 (95.5)
• Night sweat	217 (89.7)
• Arthralgia	215 (88.8)
• Fever (≥ 38 °C)	202 (83.5)
• Backache	176 (72.7)
• Headache	145 (62.5)
• Hepatomegaly	85 (35.1)
• Splenomegaly	83 (34.3)
• Weight loss	79 (32.6)
• Nausea and/or vomiting	68 (28.1)
Obstetrical symptom and signs	
• Vaginal bleedings	22 (9.1)
- Brownish	8 (3.3)
- Malodorous	8 (3.3)
- Reddish	6 (2.5)
• Vaginal bleeding plus fever (≥ 38 °C)	9 (3.7)
• Groin pelvic pain	8 (23.5)
Coexistence of other brucellar foci	113 (45.9)
• Sacroiliitis	65 (26.9)
• Arthritis	42 (17.4)
• Spondylodiscitis	12 (4.9)
• Neurobrucellosis	6 (2.5)
• Others*	5 (2.1)

Data are expressed as *n* (%).

*Clinical hepatitis, 3; respiratory system involvement, 1; urinary system involvement, 1

Table 2 Results of microbiological and serological investigations among 242 pregnant women with brucellosis

Variable	No. of (+)/no. of tested	Percent
Rose Bengal test	223/225	99.1
STA (≥ 1:160)	225/232	97.0
STA (≤ 1:80), Coombs-STA (≥ 1:160)	7/7	100.0
ELISA test results in blood samples		
• Immunoglobulin M (+)	8/10	80.0
• Immunoglobulin G (+)	8/10	80.0
Culture results		
• Blood culture*	56/134	41.8
• Abortion specimen culture	0/3	0.0
• Placental specimen culture**	2/2	100.0

Data are presented as *n*/*N* (%)

STA standard tube agglutination test

**Brucella melitensis*, 36; *Brucella abortus*, 2; *Brucella* spp., 18

***Brucella melitensis*, 2

an early diagnosis. The Peruvian study also found less OC in patients who were treated early [11]. Accordingly, we believe that prompt therapy can be life-saving for the fetus.

Blood cultures, the gold standard for laboratory diagnosis of brucellosis, were obtained in half of the patients and yielded *Brucella* spp. in two-fifths of the cases. Most of our patients were seropositive. *B. melitensis* is known to be responsible for the majority of cases, recurrences, and chronic stages in the world [1]. Among the isolates identified to the species level in this study, most of them were *B. melitensis* and this was in accordance with common data in Turkey [2, 20]. The results of this study strongly suggested that bacteremia would be associated with OCs during brucellosis in pregnancy.

Our study demonstrated several associated risk factors for OCs in this group of patients, including vaginal bleeding, nausea and/or vomiting, and oligohydramnios on USG. A strong correlation between vaginal bleeding and spontaneous abortion has previously been reported [11, 12, 16]. Prolonged gestational brucellosis has been believed to cause poor obstetric outcomes, such as preterm labor, chorioamnionitis, and placental abruption [21], and our data are consistent with that. In contrast to many other forms of brucellosis [6, 8], most of the patients in this study were diagnosed at the acute stages. The probable explanation is that brucellosis may exert an additional pressure in pregnancy, so that these patients seek medical care leading to the early diagnosis. Vaginal bleeding is a common symptom of obstetric conditions in the first trimester such as abortion and ectopic pregnancy, causing early pregnancy losses. Other symptoms of abortion are severe cramps, abdominal pain, fever, weakness, and back pain. In the second and third trimesters, bleeding can be associated with cervical insufficiency and placental disorders with adverse maternal and fetal outcomes like IFD, prematurity, and even maternal death [22, 23]. Brucellosis should be remembered during vaginal bleeding particularly in a febrile pregnant woman living in or traveling to brucellosis endemic regions since it is an independent risk factor for OCs.

Some previous reports suggest that nausea and vomiting may be the predominant complaints in patients with gestational brucellosis [27, 28]. The differential diagnosis of nausea and vomiting in pregnancy can be extensive, and the underlying cause can sometimes be difficult to diagnose [24]. Accordingly, we have seen that oligohydramnios strongly predicted an OC. Basically, oligohydramnios reduces fetal growth resulting in placental insufficiency, IFD, and fetal lung immaturity [25].

All brucellosis patients including pregnant women should receive antimicrobial therapy. Antepartum therapy with SXT or SXT plus rifampicin has been reported as protective against spontaneous abortion [12]. Ceftriaxone plus rifampicin

Table 3 Risk factors for obstetric complications (OC) in 242 pregnant women with brucellosis

Variable	Adverse ($n = 34$)	Favorable ($n = 208$)	P value
Age range (years)			
• 17–25	11 (32.4)	49 (23.6)	0.119
• 26–34	16 (47.0)	79 (37.9)	
• 35–50	7 (20.6)	80 (38.5)	
Gestational age at the time of diagnosis (weeks)			0.458
• First trimester (≤ 12)	11 (32.4)	49 (23.6)	
• Second trimester (13–24)	12 (35.2)	92 (44.2)	
• Third trimester (≥ 25)	11 (32.4)	67 (32.2)	
Clinical stage*			0.071
• Acute	30 (88.2)	200 (96.2)	
• Subacute and chronic	4 (11.8)	8 (3.9)	
History of pregnancy during brucellosis prior to this study	2 (5.9)	7 (3.4)	0.618
No. of pregnancies prior to this study			
• 0	12 (35.2)	50 (24.0)	0.333
• 1	8 (23.5)	67 (32.2)	
• ≥ 2	14 (41.2)	91 (43.8)	
No. of abortions prior to this study	4 (11.8)	12 (5.8)	0.253
Systemic symptoms and signs			
• Backache	21 (61.8)	155 (74.5)	0.146
• Hepatomegaly	14 (41.2)	71 (34.1)	0.445
• Splenomegaly	18 (52.9)	65 (31.3)	0.019
• Nausea and/or vomiting	20 (58.8)	48 (23.1)	< 0.0001
Vaginal bleeding	15 (44.1)	7 (3.4)	< 0.0001
Routine laboratory test abnormalities			
• Anemia (hemoglobin < 11 g/dL)	19 (55.9)	53 (25.5)	< 0.001
• Thrombocytopenia (platelet < 150×10^9)	1 (2.9)	6 (2.9)	1.0
• High level of serum ALT (> 63 IU/L)	8 (23.5)	24 (11.5)	0.096
• High level of serum AST (> 41 IU/L)	13 (38.2)	41 (19.7)	0.025
Blood culture positivity	12/17 (70.5)	44/117 (37.6)	0.016
Obstetric ultrasonography findings			
• Oligohydramnios	5 (14.7)	1 (0.5)	0.0002
• Placenta Previa	2 (5.9)	4 (1.9)	0.2
Coexistence of other foci of brucellosis	14 (41.2)	99 (47.6)	0.579
Drug combinations, commonly used			
• Ceftriaxone + rifampicin	12 (35.3)	80 (38.5)	0.849
• SXT + rifampicin	11 (32.4)	68 (32.7)	1.0
• SXT + ceftriaxone + rifampicin	4 (11.8)	43 (20.7)	0.348
Low birth weight (< 2500 g)	1 (2.9)	16 (7.7)	0.479

Data are expressed as n (%). Fisher's exact test and Freeman-Halton extension of the Fisher's exact test for a two-rows by three-columns contingency table compared proportions

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *SXT* trimethoprim/sulfamethoxazole

*According to the duration of symptoms, brucellosis was classified as acute (less than 8 weeks), subacute (8 to 52 weeks) and chronic (more than 52 weeks)

treatment has been shown to be most efficient compared to SXT plus rifampicin or rifampicin alone [10]. In this study, similar combinations were used and rifampicin was the most commonly preferred drug among the combinations as recommended by the World Health Organization [1]. We found no association between any of three combinations and the occurrence of OCs. Although we only found a low rate of relapse (0.4%), up to 17% of cases can relapse in the year following infection, even in successfully treated cases [10]. Although some large previous studies did not demonstrate excess maternal mortality [10, 12,

17], a recent study reported 1% of mortality among 101 women [11] and a higher range of adverse outcomes has been summarised in a recent review of published case series [26].

The major limitations of this study are its retrospective design and lack of control patients without brucellosis. It is very difficult to recruit such a large cohort of pregnant women with brucellosis prospectively. The strength of this study is the multicenter design and the largest case series of pregnant women with brucellosis, so that results can be generalized to other settings.

In conclusion, the data from this study performed in pregnant women with brucellosis demonstrated several associated risk factors for OCs. In order to manage brucellosis during pregnancy effectively, health care workers should consider brucellosis in women who have the described obstetric complications. However, brucellosis in pregnancy is a relatively milder disease than is generally perceived. We recommend that pregnant women with OC or with fever should be investigated for brucellosis if they live in or have traveled to an endemic area, and treated promptly if infection is diagnosed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. NJB is affiliated to the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Emerging and Zoonotic Infections at University of Liverpool in partnership with Public Health England (PHE), in collaboration with Liverpool School of Tropical Medicine. NJB is based at the Liverpool School of Tropical Medicine. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

Ethical approval Ethics Committee of the Fatih Sultan Mehmet Training and Research Hospital Review Board, Istanbul, Turkey.

Informed consent Not applicable. The study has a retrospective design.

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