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Seroprevalence of brucellosis infection among pregnant women

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Literature review

Brucellosis, commonly known as “undulant fever”, “Mediterranean fever” or “Malta fever” is a leading cause of zoonosis worldwide caused by the bacterial genus brucella. Brucella is an aerobic, gram-negative, non-fermenting, facultative intracellular, non-motile, non-spore-forming, cocci, cocobacilli or short rods based on DNA homology and represent a single species (1) It is transmitted to humans by direct or indirect contact with infected animals or their products (2). The entry of the organism is the conjunctiva, respiratory mucosa and damaged skin. Generally the transmission from person to person is uncommon, however the human sources of infection may occur in the following ways: vertical transmission with placental circulation, breast feeding, sexual contact, blood transfusion and bone marrow transplantation (3).

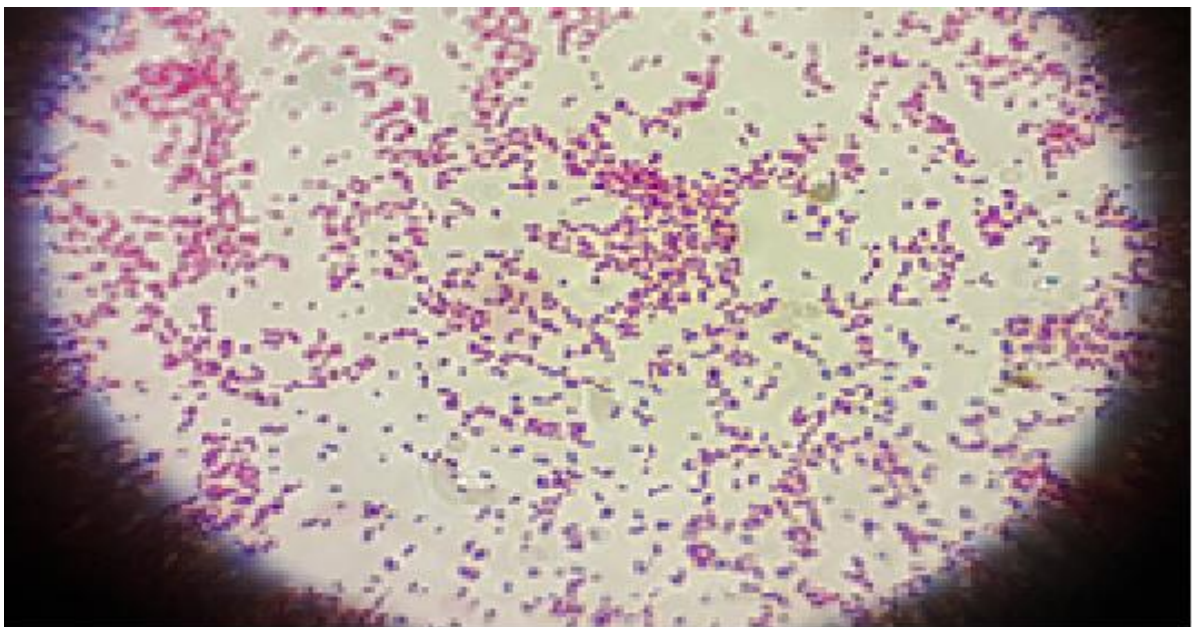


Figure 1. *Brucella* under microscope

The most common reported symptoms and signs were fever, headaches, fatigue, malaise, chills, sweats, myalgia, lack of appetite,

weight loss and arthralgia (4). The first reported brucellosis during pregnancy was in 1908 when (Malta fever), brucellosis, was clinically described (5).

Lately, spontaneous abortions in women might be associated with the isolation of brucella from an aborted fetuses placenta (6). It is believed that brucellosis causes fewer spontaneous abortions in humans than it does in animals because of the absence of erythritol in the human placenta and fetus (7). Erythritol is a constituent of normal ungulate fetal and placental tissue and, in cases of bovine abortion, promotes overwhelming infection of the fetus and placenta. Additionally, the reason for the lesser role of abortion in human brucellosis is the presence of anti-brucella activity in human amniotic fluid (8).



Figure 2. Brucella species culture

Brucellosis in pregnancy is of special interest as it remains controversial whether it is a precipitant of poor outcomes beyond congenital brucellosis. This is the first systematic review with meta-analysis analyzing whether brucellosis increases the incidence of other adverse pregnancy outcomes. if one or more women had brucellosis

detected during pregnancy and the incidence of at least one of the following outcomes was reported for all cases in the series: spontaneous abortion (SA), intra-uterine fetal death (IUFD), preterm or term live born infant, and/or congenital brucellosis. Cases were excluded if maternal brucellosis was recognized only after an infant was diagnosed with congenital brucellosis. Case series from endemic countries retrospectively seeking evidence of brucellosis in women with adverse pregnancy outcomes were also included if they described testing for minimum ten women (9).

Traditional thinking was that adverse pregnancy should be uncommon with brucellosis due to the absence of erythritol in the human placenta. This sugar is present in animal placentas and promotes *Brucella* growth (10). Another theory was that anti-*Brucella* activity in amniotic fluid would prevent infection of the fetus. However, *Brucella* has been detected from aborted fetuses. Furthermore, fetal infection is not a prerequisite for an adverse outcome as it seems likely that maternal brucellosis can precipitate abortion of a healthy fetus. Therefore, not surprisingly, the incidence of SA in women with brucellosis was about 25% (11).

Human brucellosis has an incubation period ranging from weeks to months, and has protean clinical manifestations that can wax and wane and mimic infectious and non-infectious diseases. Sustaining a high index of suspicion for infection is essential, particularly in high risk individuals living in endemic areas. Pregnancy is considered to be a high risk condition due to impaired immunological status. The incidence of brucellosis during pregnancy is not known in endemic countries as there is not routine testing. The majority of seropositive pregnant women report a history of unpasteurized milk consumption or contact with animals (12). Thus,

potential occupational exposure and family history of brucellosis should be obtained during prenatal care in endemic areas. The clinical manifestations of brucellosis in pregnancy are non-specific and similar to those in non-pregnant women; fever, chills, sweating, arthralgia, and hepatosplenomegaly are the most commonly encountered presentations (13).

Maternal bacteremia, fever and disseminated intravascular coagulation have been hypothesized to result in SA and IUFD (14). However, adverse outcomes occur in the absence of maternal bacteremia and some postulate that an allergic mechanism contributes to recurrent SAs with chronic maternal brucellosis. There are recent studies of the pathophysiological mechanism of adverse outcomes. Trophoblasts are cells that nourish the embryo and eventually develop into part of the placenta. *Brucella* has been proven to be capable of replication in trophoblasts, which could interfere with their invasive capacity, potentially related to their effect on laminin-receptor-1 (laminin are extracellular proteins that are an integral part of the structure of all tissues) (15).

Brucella has not yet been detected in human trophoblasts but such studies are difficult to perform as brucellosis is rarely diagnosed prior to abortion. Appropriate antibiotics during pregnancy appear to improve the prognosis; a 6 week course of two antibiotics is commonly prescribed but there is no consensus on the optimal choice of antibiotics (13). Pregnant women with untreated brucellosis have also been reported to be at high risk for premature rupture of membrane (PROM), chorioamnionitis, postpartum endometritis, and intrauterine growth retardation but there are no studies with a control group (12). There is no evidence that brucellosis leads to infertility. In a study from Columbia, 24 women with repeat

spontaneous abortions were found to have evidence of brucellosis and all had subsequent successful pregnancies (16).

Brucellosis is routinely misdiagnosed, or at best diagnosed incidentally; therefore, physicians in both endemic and non-endemic areas should be aware of Brucellosis and consider this disease in the differential diagnosis of febrile episodes during pregnancy. Blood culture is the reference standard for the diagnosis of *Brucella* infection in humans . The rose Bengal plate test is used as a screening serological test, and positive results are confirmed by the serum agglutination test. Other tests, such as ELISA(Enzyme linked immune assay and PCR (Polymerase chain reaction), are increasingly used for the diagnosis of Brucellosis (17).

For the treatment of brucellosis in pregnancy, rifampicin in combination with TMP-SMX for 6 to 8 weeks is the most commonly used and preferred regimen, despite the findings that the incidence of abortions among 22 patients treated with TMP-SMX monotherapy was not significantly different from that of 17 patients treated with a combination of TMP-SMX and rifampicin (18). Rifampicin is the mainstay of brucellosis treatment during pregnancy and the World Health Organization advises rifampicin monotherapy as the first line. Monotherapy is still questionable in case of brucellosis treatment and further randomized studies should give the answer whether this option is suitable for the treatment of pregnant women with brucellosis. Some authors treat brucellosis in pregnancy with gentamicin for 1 week plus TMP-SMX for 6 weeks, with or without rifampicin (19). In the study of Inan et al., 11 different regimens composed of ceftriaxone, rifampicin, TMP-SMX, doxycycline, and streptomycin/gentamicin were used and no association between any of three widely used combinations (rifampicin plus TMP-SMX, rifampicin plus ceftriaxone, and rifampicin plus TMP-SMX plus

ceftriaxone) and the occurrence of adverse pregnancy outcomes was found (20).

Another study with a small number of cases compared the treatment outcome of four different regimens including TMPSMX monotherapy, rifampicin monotherapy, TMP-SMX plus rifampicin, and ceftriaxone plus rifampicin, and the overall conclusion was that the ceftriaxone-rifampicin combination therapy was the most effective one (21). Having in mind that a significant rate of antimicrobial resistance of *Brucella* has been recently observed *in vitro* for rifampicin and TMP-SMX, ceftriaxone could also be a rational choice in the combination treatment approach and a promising regimen for treating pregnant women with brucellosis in endemic regions (22).

OTHER STUDIES AND DISCUSSION

Various studies have reported the seroprevalence of brucellosis among pregnant women with a history of adverse pregnancy outcomes from 1.8 to 25.0% (23). However, the evidence of an association between *Brucella* seropositivity and adverse pregnancy outcomes is still inconclusive from previous studies which may be due to the use of various serological tests such as the Rose Bengal Plate Test, tube agglutination or an enzyme-linked immunosorbent assay and the cross-sectional study was applied in most studies (24). To evaluate a causal relationship between brucellosis seropositivity and adverse pregnancy outcomes, a prospective study using serological diagnostic tool with high specificity for antibodies testing should be carried out. Previous studies on the history of exposure to animals and/or raw animal products prior to or during pregnancy and the association with adverse pregnancy outcomes have focused on symptomatic rather than asymptomatic pregnant women (25). The time from exposure to an infected animal to the detection of seropositivity in

humans can vary from a week up to 10 years which can be indicated acute, chronic or previous infection (26).

Brucellosis can be diagnosed when the serological results are positive which is more common in symptomatic than asymptomatic individuals. In Thailand, the rate of spontaneous abortion was 6.9% of total pregnancies (27), and rates of preterm and low birth weight newborns were 13.7% and 8.4%, respectively. However, to date in Thailand there have been no studies examining brucellosis in pregnant women and to what extent it might be related to adverse pregnancy outcomes. Understanding the factors associated with exposure to animal or raw animal products and the relation of such exposure to the pregnancy risk of brucellosis would be useful for health education and promotion (28).

A Study was conducted from September 2017 to September 2019, at Maternity Hospital, Erbil City, Iraq. Investigations for the hormonal assays and infections (toxoplasmosis) were negative. The inclusion criteria were patients with a history of three or more consecutive early pregnancy losses and patients with a history of hepatitis or brucellosis involved. One hundred and twenty women (sixty aborted and sixty healthy controls) were enrolled in this case–control study. The controls were women with normal pregnancy who were para 3 and gravida 4. The diagnosis was approved according to the clinical criteria and partial thromboplastin time. The exclusion criteria were the following: a history of uterine anomalies; diabetes mellitus; thyroid disease; aspirin, heparin, antibiotics or corticosteroid intake; embryo anomalies; chronic systemic disease including lupus, autoimmune diseases, hypertension, asthma, and cardiopulmonary diseases; and a previous history of asymptomatic urinary tract infection (29).

Anti-*Brucella* spp. antibodies were detected in two out of 307 (0.6%) and three out of 307 (0.98%) pregnant women by RBPT and cELISA, respectively. Only one out of 307 pregnant woman was seroreactive for *Brucella* spp. by both methods. All pregnant women seroreactive for *Brucella* spp. Were in the third trimester of gestational age and had a history of abortion (30).

In Sudan, 120 serum biological samples were obtained from pregnant women with abortion who attended Omdurman Maternity Hospital. Two serum samples from 120 samples were positive (1.7%) for Brucella antibodies Table (1), while the remaining serum samples (118) samples were negative (98.3%) Table (1) when used Rose Bengal test.

Table 1. Frequencies of positive and negative Brucellosis results using Rose Bengal Test pregnant women with abortion.

RBPT result	Frequency	Percent
Positive	2	1.7%
Negative	118	98.3%
Total	120	100.0%

The age distribution of seropositive and seronegative for Brucellosis ranged from less than 18 to 50 years. The seropositive result was 0.8% among Brucellosis patients in 18-28 year ages and 29-39 year ages respectively, followed by seronegative result was 0.0% in <18year age and 40-50 year age respectively (31).

Table 2. Distribution of age groups among positive and negative Rose Bengal Test Results women with abortion.

Age group	RBT result frequency			% of frequency		Total percentage
	Positive	Negative	Total	Positive	Negative	
<18	0	1	1	0.0%	0.8%	0.8%
18 – 28	1	64	65	0.8%	53.3%	54.2%
29 – 39	1	48	49	0.8%	40.0%	40.8%
40 - 50	0	5	5	0.0%	4.2%	4.2%
Total	2	118	120	1.7%	98.3%	100.0%
(P value = .985)						

Table 3. Distribution of residence among positive and negative Rose Bengal Test Results in aborted women.

Residence	RBT result frequency			% of frequency		Total percentage
	Positive	Negative	Total	Positive	Negative	
Khartoum	2	112	114	1.7%	93.3%	95.0%
Algazera	0	1	1	0.0%	0.8%	0.8%
White Nile	0	3	3	0.0%	2.5%	2.5%
Kordofan	0	1	1	0.0%	0.8%	0.8%
Naharalneel	0	1	1	0.0%	0.8%	0.8%
Total	2	118	120	1.7%	98.3%	100.0%
(P value = .999)						

Table 4. Association of positive and negative Rose Bengal Results with Level of education in aborted women.

Level of study	RBT result frequency			% of frequency		
	Positive	Negative	Total	Positive	Negative	Total percentage
Illiterate	0	10	10	0.0%	8.3%	8.3%
Basic	0	40	40	0.0%	33.3%	33.3%
Secondary	2	38	40	1.7%	31.7%	33.3%
Under graduate	0	3	3	0.0%	2.5%	2.5%
graduate	0	25	25	0.0%	20.8%	20.8%
post graduate	0	2	2	0.0%	1.7%	1.7%
Total	2	118	120	1.7%	98.3%	100.0%
(P value = .540)						

Table 5. Association of positive and negative Rose Bengal Results with history of contact with animals in aborted women.

Animals	RBT result frequency			% of frequency		
	Positive	Negative	Total	Positive	Negative	Total percentage
Yes	0	21	21	0.0%	17.5%	17.5%
No	2	97	99	1.7%	80.8%	82.5%
Total	2	118	120	1.7%	98.3%	100.0%
(P value = .511)						

In Nigeria ,The overall seroprevalence of brucellosis among the participants was 19.0%. The proportion of recent infection was 17.4% and chronic infection was 1.7% among women with miscarriage in the study. A positive relationship between age, history of previous miscarriage, consumption of milk products, consumption of roasted meat/barbecue and recent *Brucella* infection was found in this study. Chronic *Brucella* seropositivity was also found to have a positive

relationship with the number of pregnancies participants had in the past. There was, however, no relationship between the residential area, marital status, ethnic group, religion, educational level, history of pre-term birth/still-birth (32).

In Thailand, Thirty-six women with seropositive (34.3%) for antibodies against *B. abortus*, *C. burnetii*, or *T. gondii*. The seropositivity of IgG anti-*T. gondii* antibodies was highest (31.4%), followed by IgG anti-*C. burnetii* antibodies (1.9%), and IgG anti-*B. abortus* antibodies (1.0%). None of the women were found to be co-seropositive for antibodies against any of those three pathogens. Due to the small number of women with seropositivity for IgG anti-*B. abortus* and IgG anti-*C. burnetii*, the factors associated with being seropositive could be analyzed only for seropositivity for IgG anti-*T. gondii*. Women aged over 30 years or multiparous women were significantly more likely to show positive antibodies in univariate analysis, but there were no significant associations in the multiple logistic regression analysis. The higher the woman's age, the greater the odds ratios for positive antibodies in the dose-response relationship. Women with low education or who were a housewife were more likely to have higher odds of positive antibodies, but not to a significant level (33).

Conclusion

Brucellosis can be found among pregnant women with a significant frequency in endemic regions. The incidence of adverse obstetric outcomes in women with brucellosis exceeds the rates among general population. Furthermore, brucellosis during pregnancy might have a negative influence on the newborn's health and might cause delivery team infection. Early recognition of the disease and timely administration of antimicrobial therapy can significantly decrease the risk of unfavorable obstetric,

neonatal, maternal, and delivery team outcomes. Screening and education of pregnant women as well as of all women of childbearing age should be compulsory measures to prevent the disease in endemic regions for brucellosis (34).

A high seropositivity to *T. gondii* and low seropositivity to *Brucella* spp. have been found in pregnant women from Mogadishu, Somalia. Considering the high number of abortions in the country associated to the fact that awareness on other zoonotic abortifacient pathogens in Somalis is very low, further studies should be conducted to evaluate the potential causes of abortions (30).

One-third of women with adverse pregnancy outcomes showed positive antibodies for toxoplasmosis, while coxiellosis and brucellosis were less common. For toxoplasmosis seropositivity, a dose-response relationship with age was detected, and low educational attainment and being a housewife were found to be associated risk factors (33).

Brucellosis is prevalent in pregnant women and gravid domestic ruminants in Kagera Region. In this study, the abortion rate was lower compared to some previous reports in the country. Despite the statistical similarities of positivity to brucellosis in aborted and non-aborted cases, a proportion of 0.5% of the abortions was attributable to *Brucella* infections in gravid ruminant while 3.5% of abortions were attributed to positivity of the disease in pregnant women at the population level. Furthermore, positivity to brucellosis was highly associated with the exposure of the disease in pregnant women, while exposed cattle seemed to be at higher risk of contracting *Brucella* infections compared to other species. In Kagera Region, pregnant women and ruminants are at risk of *Brucella* infections which endemic prevalence could contribute to the reproductive failures recorded in these species. Results from the serological tests used

in this study are important to describe the risk for brucellosis infection in pregnant women and gravid ruminants. However, molecular tools could support more the results from serological tests to avoid interpretation from cross-reaction with other pathogen agents. Differential diagnosis of brucellosis with other infectious and febrile diseases is recommended for spontaneous abortions in humans and domestic ruminants (35).

The febrile conditions among pregnant women are alarming, so that the coordination between medicals and researches was started in this field. Brucellosis was found to be contributory factor in women with abortion in Omdurman Maternity hospital (31).

High serum ANAs are not uncommon in women with unexplained recurrent miscarriage, suggesting the possible role of an autoimmune disorder on abortion, at least in a subgroup of patients. Maternal HBV carrier status and brucellosis may be independent risk factors for miscarriage, and careful surveillance is warranted. Searching for and detecting asymptomatic bacteria and viruses may be of benefit for preventing spontaneous abortions related to high ANA levels. This study reflects the clinical reality of pregnant women and indicates that HBV carrier status and brucellosis confer substantially increased risk for miscarriage. More importantly, this type of study may provide valuable clues to guide medication and treatment regimens (36).

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