



## Brucellosis: Problems of Female and Male Organs

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### Abstract

In the hospitals of Vladikavkaz (Russia) 55 pregnant women with various clinical forms of brucellosis were examined. To identify the pathology of pregnant women with brucellosis, epidemiological history data were taken into account. The age of the sick women corresponded to the childbearing age: from 19 to 45 years. Patients with the latent course of brucellosis considered themselves healthy, but out of 39 patients, 13 had a premature birth. The reproductive system in men was also studied by analyzing 100 medical histories of patients with brucellosis (acute stage – 20, chronic – 80). We have identified orchitis with the development of dropsy, orchiepididymitis with manifestations of the disease in the form of chills, and high fever. Changes in the genitals of men with brucellosis are often the cause of diagnostic errors, in connection with which a clinical example is given for the purpose of interdisciplinary differential diagnosis with the pathology of the lesion of this system in other diseases.

**Disciplinary: Medicine.**

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## 1 Introduction

To date, brucellosis occupies a significant share among occupational diseases of infectious and parasitic nature, as it is a regional infectious pathology in regions with developed animal husbandry. Over the past two decades, from 400 to 700 patients with newly diagnosed brucellosis have been registered in the Russian Federation. The percentage of morbidity in children under 14 years of age has increased more than 3 times: from 5 to 15 cases per 100 thousand population [1].

Brucellosis infection is a regional pathology in the Republic of North Ossetia – Alania (Russia) and its relevance are determined by the variability of clinical symptoms: damage to various organs and systems (reticulogistiocytic, central nervous, urogenital, cardiovascular and locomotor apparatus). They are mainly involved in the pathological process in the acute-septic and septic-metastatic phases [2].

The purpose of the study: To study and decipher the damage to the urogenital system in women and men with brucellosis in the dynamics before and after antibacterial, antioxidant, and antiviral therapy. Identification of various complications in women of childbearing age with brucellosis in the pre-and postpartum periods and their outcomes. And in men – focal lesions of the reproductive organs. Changes in the genitals in brucellosis are often the cause of diagnostic errors, in connection with which the patient's medical history is given in order to conduct differential diagnosis with the pathology of the lesion of this system in other diseases.

## 2 Literary Review

A feature of brucellosis is a tendency to a chronic relapsing process. With the development of various clinical stages of the disease (acute, subacute, chronic, residual), inflammatory phenomena manifest themselves in various ways. In the acute stage, serous inflammation of the internal organs is detected due to increased vascular permeability, followed by dystrophy of parenchymal elements. In the subacute course, mainly productive inflammation was detected in various organs with the formation of granulomas characteristic of this infection [2-4]. At the stage of chronic development of brucellosis, processes of a productive nature prevail with the phenomena of scarring and the development of sclerotic processes in various organs and tissues. The development of a polymorphic clinical picture indicates a lesion of the body as a whole, a wave-like course with alternating periods of exacerbation and remission [2, 5].

Immunity to infections, in particular in brucellosis, is a constant "battlefield" between the host's defense mechanisms and mutating pathogens. The immune system has a variety of forms of response to antigenic effects and mechanisms that control the intensity and direction of the response: nonspecific and specific. Age-related immunity: the immunological reactivity of an early-age organism, characterized by weak production of antibodies during immunization, has been proven [6-8]. In newborns, there are no plasma cells in the bone marrow, regional lymph nodes, which are the main producers of antibodies. They appear 2-6 months after birth, and the level of gamma globulins in the blood increases only after the third month [9].

The urogenital system is often affected by brucellosis. Inflammatory processes in women and men in the genitals are detected at various stages of the disease.

The existence of resistance of an early-age organism to brucellosis is not sufficiently covered in the literature. The issues of the role of heredity, the transfer of antibodies from mother to offspring, and transplacental infection are not differentiated. There are isolated reports of the possibility of intrauterine infection of the fetus. However, there are cases when mothers who

isolated brucella with milk breastfed their newborn children, but the disease did not develop. This phenomenon is explained by the insufficient virulence of lactostamps [10,11].

### **3 The Course of Pregnancy in Patients With Brucellosis**

Our team has identified lesions of the female genital organs in the form of endometritis, oophoritis, salpingitis, mastitis, menstrual disorders in the form of dysmenorrhea. Termination of pregnancy is characteristic of chronic brucellosis, more often in terms of 3-4 months, and one of the patients we observed had miscarriages for 6 years fivefold. With a latent course, they serve as the only manifestation of the disease, especially with the usual miscarriage of pregnancy. The latter is associated with the septic effect of brucellosis infection on the body, in particular, the effect on the muscles of the uterus of toxins that cause its contraction. Therefore, if women have "causeless" abortions and gynecological diseases, brucellosis should be excluded. With this infection, the amount of progesterone, ascorbic acid, and probably a violation of prostaglandin metabolism, leading to termination of pregnancy, decreases. An important role in spontaneous abortion belongs to inflammatory changes that develop in the placenta and lead to disorders of its blood supply. If pregnancy persists, it proceeds with complications (hypochromic anemia, toxicosis of the second half). Dropsy of pregnant women and nephropathy of various degrees are frequent in patients with brucellosis, untimely discharge of amniotic fluid, weakness of labor activity develops, the severity of which depends on the severity of the brucellosis process and the degree of endometrial damage. Brucellosis develops in pregnant women as a more frequent pathology of attachment and separation of the placenta. Premature spontaneous termination of pregnancy and antenatal fetal death largely determines placentitis. Various complications were identified in women with brucellosis in the postpartum period: tight attachment of the placenta delayed afterbirth and hypotonic bleeding. Feverish reactions associated with an exacerbation of the brucellosis process caused by childbirth are also not uncommon. At the same time, endometritis and subinvagination of the uterus are noted [12].

The antenatal infection of the fetus in the gynecological and infectious diseases clinics of the North Ossetian Medical Academy at the Vladikavkaz Emergency Hospital was deciphered by our team (brucelles were isolated from the tissues of dead fetuses, amniotic fluid, placenta and membranes).

We also observed a significant number of cases of causeless abortions, premature birth, miscarriage and intrauterine fetal death, which served to study these causes: during the examination, most women were diagnosed with brucellosis.

### **4 Method**

During the period 2015 to 2019, 55 pregnant women with brucellosis were under our supervision (in the clinic of infectious diseases, maternity hospitals, gynecological clinic and women's consultations in Vladikavkaz, Russia). Of these, there were 21 primiparous (including 5 primiparous), 34 repeat-bearing. In the period from 1 to 2 years, 23 women were ill with brucellosis, from 2 to 7 years – 32.

Epidemiological history: - the professional composition of women pregnant with brucellosis: milkmaids – 11, workers of meat processing plants – 19, collective farmers in farms of large and small cattle – 18, housewives – 19, employees – 8. The age of the patients was 19 – 45 years. The patients were examined according to Wright's reactions in dilutions of 1:200 to 1:800 – 20, Hedderson – Kaitmazova – 0.04 – 21. Delayed hypersensitivity was determined (Burne test). It turned out to be positive in 38 patients. There were 7 patients with acute brucellosis, 3 with subacute, 42 with chronic, and 3 with residual.

The outcome of pregnancies with brucellosis is presented in Table 1. Statistical data processing was carried out using Fortran and Matlab software [13,14].

**Table 1:** The outcome of pregnancies with brucellosis.

Total number of patients	Primiparous	Repeat births	Number of spontaneous abortions		Number of premature births
			Pre - pregnant	Repeat pregnancies	Repeat pregnancies
55	20	22	-	1	2

## 5 Result and Discussion

In the treatment of patients with acute and subacute stages of brucellosis of women with significant symptoms of various lesions of the female genital organs, complex antibacterial therapy was used. The most effective were combinations of doxycycline + rifampicin according to an intermittent cyclical scheme of 10-12 days with breaks of 7-10 days, 2-3 courses with a change of antibiotics: fluoroquinolones (levofloxacin + cotrimoxazole), taking into account contraindications (children under 18 years of age, pregnancy, lactation, and should also avoid insolation and the development of the Herxheimer reaction. Glucocorticoids for 5 days, 20 mg 3 times a day, were prescribed for the severe course of the disease. As an antioxidant therapy (galavit 200mg 2p per day, then 100mg every other day for 15 days, aevit for 10 days, as well as cycloferon (immunomodulator), which reduced intoxication syndrome, joint pain, and in men – scrotum organs and a significant effect on improving the state of spermatogenesis. A decrease in the amount of progesterone and ascorbic acid served as the basis for the inclusion of multivitamin complexes in syndrome therapy and increased detoxification. In the stage of chronic brucellosis, the therapy of female and male genital organ lesions with these drugs was corrected without the inclusion of antibiotics. Nonsteroidal anti-inflammatory drugs and physiotherapy (diathermy, UHF, paraffin applications) were widely used according to indications and models developed on rams [15,16]. Balneotherapy in remission. The outcome of pregnancies in women with brucellosis before and after treatment is presented in Table 2.

**Table 2: Pregnancy outcomes in women with brucellosis before and after treatment.**

Stages of the disease	Number of patients		Spontaneous abortions (number of patients)		Premature birth (number of patients)	
Acute brucellosis	5	2	3	1	2	1
Chronic locomotor-neurogenital form stage of subcompensation	44		10	6	10	1
Residential	6		2		3	-
Total	55	2	15	7	15	2

Spontaneous abortions in women with brucellosis were manifested by exacerbations of the main process. Subjectively: headache, pain in muscles and joints, bones, chills with an increase in body temperature from 37,3C – 38,0C, which sometimes has an undulating character. Objectively: micropolyadenitis in 11, hepatolienal syndrome in 17. It should be noted that some women after abortions have long-term discharge due to changes in the endometrium.

The mechanism of termination of pregnancy was explained by the indicators of pathomorphological examination of placentas: the inflammatory process was detected not only in the endometrium and maternal placenta but also in the villous membrane with edema, leukocyte infiltration, hyalinization of stroma, necrosis. Vascular manifestations in the form of multiple hemorrhages were also noted. These changes caused premature birth or fetal death. Indicators are also significant: late toxicosis, premature and early rupture of the fetal bladder. The placental increment was 5-6 times more common in women suffering from brucellosis than in healthy pregnant women, explained by inflammatory and degenerative changes in the placenta and uterine mucosa. Thus, brucellosis infection leads to a violation of pregnancy at various times, antenatal fetal death, premature detachment of the baby's place, and placenta previa. In this regard, if causeless abortions occur in pregnant women, they should be examined for brucellosis. Termination of pregnancy in women with brucellosis occurs more often at 2-3 months of pregnancy. Spontaneous termination of pregnancy is, as a rule, the leading, and sometimes the only clinical manifestation of brucellosis. Infection of the fetus can occur during pregnancy through the placenta and during childbirth. However, the negative effect of the mother's disease on the fetus can be without the introduction of brucella into the fetus, explained by prolonged intoxication, and sensitization of the mother's body negatively affecting the developing organism. At the same time, newborns show dry skin, a sharp decrease in body weight, subfebrility, lethargy, physiological jaundice, dyspeptic disorders have developed [17-20].

Although bacteriological studies have revealed that in patients with brucellosis, the pathogen is detected after childbirth and in milk, the question of feeding newborns by such mothers is debatable. It was revealed that serological reactions with breast secretion serum are more often positive and give a higher titer than with blood serum. But infants are very rarely infected with brucellosis. According to the authors, this is due either to the presence of passive immunity in children or to the weak virulence of the brucella lactoculture. In addition, in infants with brucellosis, it is difficult to find out whether infection occurred in utero or after childbirth through milk [21].

Studies conducted by our team have shown that intrauterine infection of the fetus from the mother is possible, brucella was also detected in the milk of a mother suffering from brucellosis, but the disease is not registered in young children, which is apparently due to the low virulence of lactostamps, and the fact that brucellosis is a zoonotic infection and without repeated passivation of pathogens through the animal's body the process cannot manifest. The cause of intrauterine fetal death, habitual early termination of pregnancy should be considered a specific lesion of the mother's urogenital organs and prolonged intrauterine intoxication of the fetus. The presence of immunological shifts in the body of children could not be established, because according to the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing in the Republic of North Ossetia-Alania for two decades, brucellosis disease was registered in women of non-childbearing age and was not recorded in young children.

The current course of brucellosis has undergone changes and is characterized by variability of clinical symptoms.

## **5.1 Cases of Brucellosis in Men**

Lesions of the genitals in men in the form of orchitis, epididymitis were detected in 12-19% of cases, swelling of the scrotum, enlargement and soreness of the testicles were detected by them in the acute stage of brucellosis in 1.5% of men. Focal lesion of the reproductive organs in men develops within a year from the onset of clinical manifestations of brucellosis. There may be a single or bilateral lesion of the testicles and appendages. Unilateral testicular infection can lead to aspermia and oligospermia and infertility [22].

When analyzing 100 case histories of patients with brucellosis (20 - acute, 80 – chronic), we diagnosed orchitis with the development of dropsy (hydrocele) in 2 patients. In 5 patients – orchiepididymitis, accompanied by chills, high fever, severe pain in the affected testicle, enlarged to the size of a goose egg, dense consistency. The skin of the scrotum is hyperemic, with a local T, the folds are smoothed. According to modern scientists, changes in the genitals in brucellosis are often the cause of diagnostic errors.

Clinical example: patient N., 41 years old, diagnosed with subacute brucellosis. After physical exertion, the patient developed a sharp pain in the right testicle, body temperature - 40C, headache, profuse hyperhidrosis, chills, and joint pain. St.Localis: enlargement of the testicle on the right, soreness during palpation, the skin of the scrotum is stretched, hyperemic. There are no dysuric disorders. Diagnosis: abscessing orchitis. The patient was operated on.

Our team conducted a study of the state of the pro-oxidant system and antioxidant protection in patients with chronic brucellosis with lesions of the female genital organs in order to correct therapeutic measures using galavit.

To assess the state of the antioxidant system in the blood of patients, the level of ceruloplasmin (CP) was determined using the method described by Rzhepakovsky et al. (2022) [23]. Ceruloplasmin is a copper-containing protein that has the properties of a ferroxidase enzyme and is

therefore involved in the oxidation of divalent iron with oxygen in the air. The synthesis of plasma ceruloplasmin is carried out mainly by liver cells, and the maintenance of its level in the blood is controlled by a number of hormones and mediators of the immune system. The CP functions in plasma and inactivates free radical oxygen forms, protecting them from the damaging effects of lipid-containing biostructures [24,25].

60 patients with chronic brucellosis with urogenital form aged from 26 to 45 years were under observation. The diagnosis was established on the basis of clinical and epidemiological data, serological reactions of Wright, Hedderson, RPGA, ELISA. The main clinical manifestations were: sweating, arthralgia mainly of large joints, cognition, an increase in body temperature to subfebrile figures, disorders in the reproductive system of women and men. The level of ceruloplasmin in the blood serum was determined by a spectrophotometrically modified Rabbinic method, during the period of the peak, extinction of symptoms and early convalescence [26,27]. Some indicators of the prooxidant and antioxidant systems in patients with chronic brucellosis (Table 3).

**Table 3:** Some indicators of the prooxidant and antioxidant systems in patients with chronic brucellosis

The studied indicator	Study period	n	X min – X max	X ± m	P
ceruloplasmin	Control group (healthy)	26	249-663	418±12,8	
	I	60	182-461	334±6,9	P<0,001
	II	55	216-475	361±5,9	P<0,001
	III	55	224-504	392±5,3	P>0,05
Malondialdehyde	Control group (healthy)	26	3-9	5±0,2	
	I	60	6-13	9±0,2	P<0,001
	II	56	3-11	7±0,2	P<0,001
	III	52	3-8	6±0,2	P<0,001

Studies conducted in patients with chronic brucellosis revealed a significant decrease in the activity of ceruloplasmin with a maximum value in the period of the height of the disease ( $334 \pm 6.9$  mg / l; P0,001). Against the background of the therapy, a second study was conducted (on the 10th – 15th day), which corresponded to the period of extinction of clinical symptoms (reduction of pain, sweating, weakness, headaches), a gradual increase in CP activity was noted ( $361 \pm 5.9$  mg/l; P0,001). In the III period, the indicators approached those in the control group (donors) ( $418 \pm 12.9$ ), consisting of healthy individuals, but remained below the normal level ( $392 \pm 5.3$  mg / l; P0.05)

As a result of the studies conducted in patients with chronic brucellosis, significant inhibition of ceruloplasmin activity in the blood was observed with a maximum value of the period of the height of the disease and the increase to the period of early convalescence.

Thus, in chronic brucellosis, a decrease in antioxidant protection was found, depending on the period of the disease, the severity of the pathological process, the presence of concomitant diseases.

Thus, the differential diagnosis of brucellosis and gonorrhea orchoepididymitis, despite the similarity of symptoms (pain in the scrotum, hyperemia of the skin, enlargement of the appendage

on the affected surface, testicular enlargement, high fever), require correction. Patients with gonorrhoeic orchiepididymitis were examined: dysuric phenomena with symptoms of urethritis, prostatitis and pathology in the urine, often abscessing in the testicle with pus, were noted. With brucellosis, they are absent, orchiepididymitis occurs against the background of a general disease. Objectively: polymicroadenopathy, intense polymyarthralgia, persistent hyperhidrosis, epidemiological history and serological data [28-33].

Thus, brucellosis is an infectious – allergic disease of a toxic – bacteremic nature, occurring as chroniosepsis with damage, along with the central, cardiovascular systems, parenchymal organs, and human urogenital organs.

## 6 Conclusion

The defeat of the female reproductive system in patients with brucellosis in the form of pregnancy disorders at various times, antenatal fetal death, as well as the development of endometritis, oophoritis, mastitis, placentitis, and causeless abortions are reflected in the example of 55 pregnant women before treatment and during the period of convalescence. The defeat of the reproductive organs in the study of 100 medical histories of men with brucellosis was revealed in the form of the presence of orchitis, orchiepididymitis, prostatitis. Focal lesions developed within a year from the beginning of clinical manifestations. Complex therapy (antibiotics, antioxidants (galavit), antiviral drugs (cycloferon) for women with brucellosis with lesions of the female and male genitalia led to an improvement in inflammatory processes.

## 7 Availability of Data and Material

Data can be made available by contacting the corresponding author.

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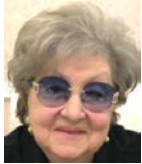
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