Toxoplasmos

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ABSTRACT

Introduction: Toxoplasmosis is a disease caused by the protozoan parasite Toxoplasma gondii, which can affect several organs and systems of the human body. It is a common infection worldwide, and it is estimated that about one-third of the world's population has already been infected. Objective: The objective of this chapter is to provide information about Toxoplasmosis, including the etiological agent, forms of contamination, treatment and diagnosis, but also how to control it. Etiologic agent: Toxoplasmosis is caused by the protozoan Toxoplasma gondii, an obligate intracellular parasite. It has a heteroxenous life cycle, with two types of hosts, humans and felines being the most common. Evolutionary forms: Throughout the biological cycle, this parasite goes through three evolutionary forms: tachyzoites, bradyzoites, and oocysts. Tachyzoites are found in the acute phase of infection, while bradyzoites are found in the chronic phase and oocysts are the forms eliminated in the feces of felines. Forms of contamination of human beings: The main form of contamination of humans occurs through the ingestion of food or water contaminated with oocysts present from the feces of infected felines, especially cats. In addition, contamination can also occur through the ingestion of raw or undercooked meat from infected animals, by contaminated blood transfusion, and by vertical transmission. Biological cycle: The biological cycle of T. gondii involves two hosts: the definitive (felines) and the intermediate (humans and other animals). In the definitive host, the parasite reproduces sexually, with the formation of oocysts that are eliminated in the feces. Clinical manifestations: The clinical manifestations of toxoplasmosis vary according to the host's immune system. In immunocompetent individuals, the infection is usually asymptomatic or oligosymptomatic, and is often confused with other infectious processes. In immunocompromised individuals, such as HIV patients, transplant recipients, and cancer patients, symptoms may be more severe, especially affecting the central nervous system. In addition, congenital toxoplasmosis can lead to a number of complications in the fetus and newborn, including chorioretinitis, brain calcifications, delayed neuropsychomotor development, among others. Diagnosis: The diagnosis of toxoplasmosis is mainly made through laboratory tests, such as the detection of specific antibodies in the blood (IgM and IgG) and molecular tests to identify the parasite's DNA. Treatment: Treatment of toxoplasmosis varies depending on the severity of the disease and the patient's immune status. In mild or asymptomatic cases, treatment is usually not required. In severe cases or in immunocompromised patients, antiparasitic drugs are used, such as the combination of sulfadiazine and pyrimethamine. Infected pregnant women also need to be promptly treated. Prophylaxis: Toxoplasmosis prophylaxis involves preventive measures such as proper food hygiene, avoiding the consumption of raw or undercooked meat, washing hands after contact with cats, and maintaining daily cleaning of cat litter boxes. Conclusion: The chapter provides a comprehensive overview of toxoplasmosis, a disease caused by Toxoplasma gondii, which can cause several consequences to humans. The comprehension of the themes addressed within the chapter promotes a better coping with this parasitosis.

Keywords: Toxoplasmosis, Toxoplasma gondii, Obligate intracecell parasite, Pregnant.

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INTRODUCTION

The discovery of *Toxoplasma gondii*, a protozoan that causes a disease widely distributed throughout the world, occurred at the beginning of the twentieth century and was carried out simultaneously in Brazil and Tunisia. Other important protozoa were also discovered during this period, such as *Giardia lamblia*, *Entamoeba histolytica*, *Leishmania* sp., among others, contributing to the knowledge of medical protozoology. The name "Toxoplasma" is derived from the Greek, meaning "bow" and "body". Subsequently, studies involving this parasite revealed the wide distribution of *T. gondii* in different types of animals and the possibility of congenital transmission.

ETHIOLOGICAL AGENT

Toxoplasma gondii is an obligate intracellular protozoan and causative agent of toxoplasmosis, a highly disseminated zoonosis with wide geographic distribution, being one of the most common parasitic infections in humans in the world. This parasite belongs to the phylum Apicomplexa and family *Sarcocystidae.* The phylum Apicomplexa is characterized by the presence of the apical complex, containing specialized secretory organelles, which are important for cell invasion in the host. Despite being a protozoan capable of invading several nucleated cells of the human body, it has tropism for some cells, such as monocytes, muscle cells, and nerve cells. Whatever the route of entry and the infective form, it is preferentially in the cells of skeletal muscle tissue and the central nervous system that tissue cysts are formed, where the parasites, in the form of bradyzoites, survive protected from recognition and destruction by the host's immune system.

It has a heteroxenous life cycle, where it has two types of hosts, performing asexual reproduction, which occurs in most animals, and sexual reproduction occurring exclusively in felids. Throughout the biological cycle, this protozoan can take three evolutionary forms: tachyzoites (a form of rapid multiplication in the acute phase), bradyzoites (a form of slow multiplication, found within tissue cysts, in the chronic phase) and sporozoites, a product of the parasite's sexual reproduction (a form found in oocysts).

HOSTS

DEFINITIVE

Felines are the only hosts where the parasite reproduces sexually, with the formation of immature oocysts that are eliminated into the environment with their feces. In the vertebrate, the intestine is fundamental in the *T. gondii* cycle, because when the protozoan reaches the intestinal mucosa it faces an immunological barrier characterized especially by the presence of IgA, which plays a fundamental role in fighting the oral infection of *T. gondii*, and also a physical barrier formed by enterocytes. To overcome the physical barrier, the parasite developed several strategies for

adhesion and invasion of enterocytes and dissemination beyond the epithelium. The enteroepithelial cycle of *T. gondii* occurs inside enterocytes and inside goblet cells of felines. Enterocytes rupture during oocyst shedding and the intestinal barrier is compromised.

Cats that do not move outdoors are less likely to have toxoplasmosis, consequently decreasing the prevalence in humans. However, environmental contamination by oocysts is very high, a factor that contributed to the high rate of seropositivity worldwide, since soil contaminated by the parasite is a source of infection that is difficult to control.

INTERMEDIARY

Intermediate hosts are considered warm-blooded animals, such as cattle, pigs, horses, birds, humans, among others. In these animals, the *T. gondii* It has an extraintestinal cycle that results in the formation of tachyzoites or bradyzoites.

In Brazil, seroepidemiological studies in humans have shown a high prevalence of infection, but relatively low pathogenesis in these hosts. In general, approximately 80% of infected people will have the asymptomatic form of the disease, depending on several factors, such as age, eating habits, housing (rural or urban), and cultural patterns. In addition, within these hosts, the group of pregnant women constitutes an important portion of the population and the risk of fetal transmission depends on factors such as the maternal immune response, the gestational age at the time of infection and the virulence of the parasite, and the transmission and severity of the case will be directly related to the gestational age.

EVOLUTIONARY FORMS

Toxoplasma gondii is a protozoan capable of parasitizing all nucleated cells of the host. It has three evolutionary stages, all three of which are capable of infecting vertebrate animals, including humans. They are: tachyzoite, bradyzoite, and oocyst.

TAQUIZOÍTO

The term 'tachyzoite' (tachymite = 'fast' in Greek) was coined in 1973 to describe the evolutionary stage of the parasite that multiplies rapidly within many cell types of the intermediate hosts and in the non-intestinal epithelial cells of the definitive host.

Tachyzoites are elliptical in shape, with an elongated shape, with their anterior region at the end and the posterior region rounded, 6 µm long and 2 µm wide. Structurally, it is formed by a trimembrane film and has several organelles, an apical complex with several structures, and a nucleus in the center of the parasite cell. In addition, they do not have the means of locomotion, but they can move by sliding, flexing, undulating and rotating. Because they are obligatorily intracellular

parasites of all nucleated cells, they are able to invade cells preferentially by active penetration, where they are then found inside parasitophore vacuoles. The multiplication of these forms occurs by endodiogenesis, which is characterized by being a specialized form of asexual reproduction. Once replication has ceased, tachyzoites complete their lytic cycle: they leave the vacuole and reach the extracellular medium through the disruption of the plasma membrane of the host cell, disseminating through the hematogenous or lymphatic route to various tissues. Tachyzoites correspond to the stage responsible for the acute phase of infection.

BRADIZOITE

The main biological characteristic of this infectious form is the ability to reproduce slowly (bradi = slow in Greek). The events that follow after the differentiation of the bradyzoites are the morphological alterations of the membrane and matrix of the parasitophore vacuole, constituting the cystic wall and giving rise to the tissue cyst, a characteristic structure of the chronic phase of the infection. So, structurally they have the same organelles as tachyzoites, but their nucleus is closer to the posterior extremity. They are approximately 7 μm long by 1.5 μm wide and are present inside cysts, which are formed by an elastic and thin cystic wall.

Tissue cysts vary in size depending on the age, host cell, and strain of *T. gondii*. The young can measure about 5 μm in diameter and contain only two bradyzoites, while the older ones can contain hundreds of organisms, reaching an average of 60 μm in diameter. They are prevalent in muscle and nerve tissues, including the brain, retina, and skeletal and cardiac muscles. The cystic wall, i.e., the structure of the cyst, provides a physical barrier against the host's immune system, characterizing the chronic phase of the disease. These forms can persist throughout life or be reactivated, such as in immunosuppressed individuals.

OOCYST AND SPOROZOITES

Oocysts contain the infective forms of *T. gondii*, the sporozoites. Each oocyst contains two sporocysts containing four sporozoites each. These sporozoites are about 8 μm long by 2 μm wide and, ultrastructurally, are similar to tachyzoites, although they have a subterminal nucleus and a greater abundance of some organelles.

Infectious oocysts are oval in shape and measure 11 x 13 μm. They have a double wall rich in proteins that acts as a barrier, preventing the sporozoites inside from suffering physical and chemical attacks. They are produced in the intestinal epithelium of felids (definitive hosts) and eliminated, still immature, along with feces in the environment, where they undergo maturation. The maturation phase can last from one to five days and depends on adequate oxygenation, humidity, and temperature. They are highly resistant structures to the environment, remaining viable in sandy and

moist soils for up to a year or more. The formation of these oocysts occurs through sexual reproduction or enteroepithelial cycle exclusive to domestic cats and other felids Under natural conditions, domestic cats can eliminate oocysts after a primary infection for up to three weeks, thus being considered important disseminators of the parasite.

FORMS OF CONTAMINATION

Toxoplasma gondii can infect humans from any of its evolutionary forms.

Horizontal transmission occurs through the accidental ingestion of oocysts present in water, fruits, vegetables, or even from contaminated hands.

Another form of infection is the ingestion of bradyzoites through the consumption of raw or undercooked meats from infected intermediate hosts, since this form is lodged in the skeletal muscles of animals such as cattle, pigs, and sheep.

Contamination can also occur from blood transfusion, when the donor is in the acute phase of the disease or at a time of re-aggravation. Vertical transmission occurs when the pregnant woman acquires primary infection during pregnancy, and then tachyzoites cross the placental barrier from the maternal circulation and reach the fetus. The risk of maternal-fetal transmission is around 40%, increasing with the advancement of pregnancy, as it depends on placental blood flow. Other factors are also involved with the potential of this transmission, such as parasite virulence, genetic susceptibility and parasite load. In the first trimester of pregnancy, this infection can lead to more serious lesions. At this stage, about 6% to 14% of neonates infected with *T. gondii* will present severe clinical forms, which may progress to fetal death. When the infection occurs in the second trimester, the main permanent sequelae are recorded, such as mental retardation, alteration of the cranial volume (micro or hydrocephalus), among others. When the maternal infection occurs in the last trimester, 59% to 72% of the NB present subclinical manifestations and, although it is more frequent, it is less severe. Therefore, during pregnancy there is an increase in the risk of vertical transmission and a reduction in the severity of fetal involvement. Women who are seropositive before pregnancy usually do not transmit it to the fetus, however, tissue cysts in quiescence from past infection (before pregnancy) can restart the life cycle of the parasite in immunocompromised pregnant women. There is no evidence to prove the transmission of the protozoan through breastfeeding, so it is not indicated to suspend breastfeeding in cases of toxoplasmosis.

BIOLOGICAL CYCLE

The development of the cycle begins when the cat, the definitive host, becomes infected with any of the three forms of the parasite. These undergo the action of the digestive juice and are released into the intestinal tract, and then invade the enterocytes of the intestinal mucosa of felines and can

guide themselves through three pathways. The first route is when asexual reproduction occurs in these cells, due to endodiogenesis and schizogony, forming the enteroepithelial cycle, and promoting the formation of more infective forms and consequent infection of more enterocytes.

The second pathway usually occurs after the asexual phase, in which the infective forms will differentiate into gametes, giving rise to macrogametocytes (female gametes) and microgametocytes (male gametes). The female gametes are immobile inside the intestinal epithelial cells, while the male gametes undergo several divisions and form 10 to 21 biflagellated microgametes that become mobile and manage to fertilize the macrogametocytes, giving rise to a rigid and resistant form, called a non-sporulated oocyst that can be released into the intestinal lumen after the rupture of the cell of origin. Thus, they reach the external environment along with the feces, but still immature. After being excreted, the oocysts undergo sporulation in the environment, becoming infectious. Oocysts, after being eliminated by felines, are easily spread by the environment in various ways, such as: by wind, water, farm animals and some arthropods. In the environment they can infect water, surface, soil, agricultural products, fruits, vegetables, surviving for long periods of time.

The third route is the rapid penetration of the infective forms, after their release through gastric juice, invading and proliferating in macrophages and other cell types, occurring up to 8 hours after ingestion. This process can be carried out both in definitive hosts and in intermediate hosts, representing the mechanism of human infection, since the first two routes only occur in the definitive host. In this type of invasion, the infective form invades the host directly, where each tachyzoite, sporozoite or bradyzoite will multiply rapidly and may penetrate several cells of the infected organism forming a cytoplasmic vacuole. Inside it, the parasite will go through successive divisions forming new tachyzoites that consequently rupture the cytoplasmic vacuole, in order to be released to infect new cells or spread through the bloodstream, reaching various regions of the body.

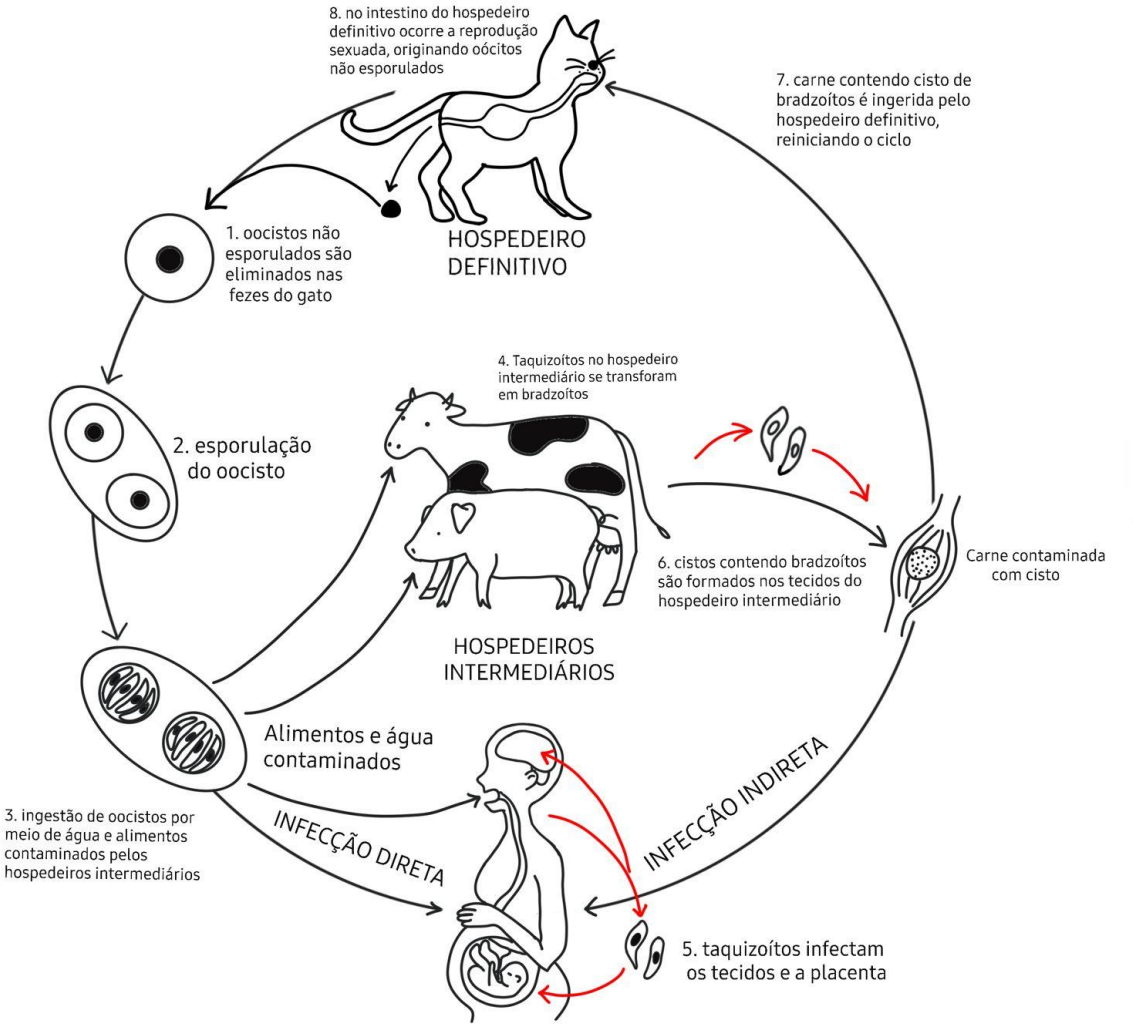
The immune response, especially cellular immunity, is always essential to stop the infection. The humoral response is also intense and relatively rapid, promoting high titration of antibodies, especially IgM and IgG.

The tachyzoites, after invading the cells and their initial proliferation, develop a cystic capsule, decrease their metabolism and, thus, transform themselves into bradyzoites, settling in host tissues, preferably within long-lived cells, such as those of the central nervous system (CNS) and skeletal muscles. In these tissues, these forms do not suffer the action of the immune system and can remain in these places for months, years and even decades, configuring themselves as forms of resistance that can be ingested later by felines or by the various intermediate hosts. In addition, factors such as the pressure of the immune system, environmental stress, among others, favor the differentiation of tachyzoites into bradyzoites. These tissue cysts occasionally rupture releasing bradyzoites that can evolve into tachyzoites and restart the infection process of neighboring cells, if

the host has a compromised immune system, this process of release and proliferation of the protozoan will be much more efficient.

Figure 1 shows a schematic drawing of the biological cycle of T. gondii and the possibilities of contamination of humans.

Figure 1 – Schematic drawing of the evolutionary cycle of Toxoplasma gondii and the routes of contamination in humans.



Source: Prepared by the authors.

CLINICAL FORMS

The clinical manifestations of toxoplasmosis are associated with the immunological competence of the host, so it is expected that most immunocompetent individuals are asymptomatic, although they may have mild symptoms, as well as in viral conditions. Thus, during the acute phase of the disease, 10 to 20% of those infected may manifest symptoms in the forms of linfoglandular, meningoencephalitis, pneumonitis, hepatitis, myositis, rash and chorioretinitis. The lymphogranular form is the most common, and usually causes lymphadenopathy with swollen lymph nodes of normal consistency, soft, elastic and little painful to palpation. The other manifestations are rarer and are

usually associated with the severe form of the disease or immunocompromised patients. Chronic infections, represented by tissue cysts, affect more the retina, nervous system, and skeletal muscles.

In immunocompromised individuals, such as HIV-positive individuals, transplant recipients, or cancer patients, symptoms can be more severe and commonly affect the nervous system, causing meningoencephalitis. Patients with this type of neurological infection may present: fever, headache, hemiparesis, hemiplegia, mental confusion, seizures, lethargy, and may progress to death. In addition, in these patients, the process of reinfection and/or reactivation of the cysts is recurrent, as well as pneumonitis and ocular toxoplasmosis are also more frequent in this population.

Regarding congenital transmission, the course of the disease will depend on the period in which the acute maternal infection occurred. Among the symptoms that the fetus may present, the following stand out: chorioretinitis, cerebral calcifications, changes in the head circumference, intrauterine growth restriction, hydrocephalus, retinochoroiditis, fetal malformations, and may also culminate in prematurity, fetal death or miscarriage. These signs can also be observed in newborns. Other signs that babies may present are related to neurological development and its functionalities. These are alterations related to the nervous system: delay in neuropsychomotor development and mental retardation, retinochoroiditis, hearing impairment and brain calcifications. They may also present with motor abnormalities, strabismus, seizures, hepatosplenomegaly, edema, myocarditis, jaundice, anemia, and skin rashes.

DIAGNOSIS

The diagnosis of *T. gondii* infection can be made by associating the clinic with laboratory methods, which can be performed by means of parasitological or immunological tests. Serology is usually the most used method, whether by public or private laboratories, as it allows the definition of infection, clinical phase and inclusion in treatment in order to minimize the associated risks, especially when it comes to pregnant women.

These serological methods are often used to diagnose the disease, as they allow the detection of the presence of anti-T. *gondii* *immunoglobulins* (IgG and IgM) that appear after infection, induced by the individual's humoral response. In the acute phase of the infection, IgM (immunoglobulin M) is initially produced, followed by the production of IgG (immunoglobulin G), which usually indicates a stage of immunity. So, a patient who has IgM negative and IgG positive is an immunized patient who suffered infection more than 6 months ago. However, individuals with negative IgM and negative IgG indicate that there has never been contact with *T. gondii*, and if in this case it is a pregnant woman, the following actions are necessary: to instruct the pregnant woman about the disease, modes of infection and avoid contamination. In addition, new tests for toxoplasmosis should be performed in the second and third trimesters of pregnancy.

In serology, a positive IgM result and a positive or negative IgG result indicate test positivity, since the presence of the IgM antibody confirms an acute T. *gondii* infection. In view of this result, the proposed therapy is initiated. In pregnant women, when there is a suspicion or confirmation of acute infection, the first action is to start treatment using spiramycin or clindamycin, which will be continuous until the end of pregnancy. In cases of indeterminate results in pregnant women, to confirm the diagnosis of acute infection by the protozoan, the avidity test for IgG is performed. In acute infection, IgG antibodies bind weakly to the antigen (low avidity) and in chronic infections, they bind strongly to the antigen, resulting in high avidity.

The diagnosis of congenital toxoplasmosis in the first year of a child's life aims to reduce the damage caused by the disease, especially visual and neurological damage. The newborn screening test for toxoplasmosis (IgM screening by capillary blood capture method), despite being indicative of infection, is not considered for diagnosis, and the result needs to be confirmed by more sensitive and specific serological tests. If the child presents with clinical manifestations suggestive of congenital infection, toxoplasmosis should be investigated, even in the face of a negative newborn screening test. And in the presence of maternal toxoplasmosis, with the possibility of congenital toxoplasmosis, the newborn needs to be fully investigated before discharge from the maternity ward, not waiting for the neonatal screening test.

TREATMENT

The treatment proposal is differentiated for each group of individuals according to susceptibility to the disease. In adults, when in the absence of another disease that compromises the immune system, the treatment is carried out based on the symptoms that the patient presents, as long as there are no complications, since treatment with specific medication can offer different levels of toxicity, if used for a long time. In individuals with compromised immune systems, the indication is a triple regimen consisting of sulfadiazine, spiramycin, and pyrimethamine or sulfadoxine. Another drug treatment proposal is the association of pyrimethamine with clindamycin, clarithromycin or azithromycin.

In pregnant women, treatment is indicated from the moment of diagnosis until the birth of the baby. The treatment indicated by the Brazilian Society of Pediatrics and the Ministry of Health is divided into two stages: up to 18 weeks, the treatment should be performed with spiramycin. After this period, if the pregnant woman is infected or with a high suspicion of infection, sulfadiazine, pyrimethamine and folinic acid should be combined. Regardless of the period in which the infection occurred, treatment should last until the end of pregnancy. Newborns of mothers infected during pregnancy, diagnosed with congenital toxoplasmosis or not, should receive treatment for 12 months regardless of the presentation of signs and symptoms. The medications used will be the same as those

indicated for the treatment of pregnant women, but in doses appropriate for the age group. If, in addition to the history of birth, the child has retinochoroiditis or severe central nervous system involvement, it will be necessary to associate prednisone or prednisolone. The goal of long-term treatment is to minimize late sequelae and promote a better quality of life.

PROPHYLAXIS

Toxoplasmosis, as mentioned at the beginning of the chapter, is a common zoonosis in humans, so it can affect adults, pregnant women, and babies. Therefore, in order to prevent contamination in pregnant women and other susceptible individuals, it is necessary to take personal hygiene measures, proper washing of food, and not to eat raw and undercooked meat. You should also drink treated, boiled or filtered water. In addition, it is important not to have contact with areas where cats can defecate, such as sands and gardens, in addition to avoiding direct contact with the feces of these animals. There are also measures related to the health of pregnant women, such as: serological screening and adequate guidance for those who do not have immunity, in addition to prenatal care.

In addition to the measures listed above, the control of blood banks and health education are indispensable.

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