

The approach to neonatal congenital infections – toxoplasmosis and syphilis

Abordagem neonatal nas infecções congênitas – toxoplasmose e sífilis

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ABSTRACT

The infections that affect the binomial mother-son during pregnancy are of great concern to obstetricians and pediatricians because of its frequency and difficulty in reaching an etiological diagnosis that is important for early treatment. Most newborns with congenital infection are asymptomatic; this shows the importance of laboratory screening for diseases that are transmitted during the pregnancy-puerperal cycle of women. This review aims to provide recommendations with regard to congenital infection by *Treponema pallidum* and *Toxoplasma gondii*. Syphilis is one of the diseases with the highest rates of mother-to-child transmission and is a public health problem still with insufficient control in the country. The diagnosis of maternal infection, performed with VDRL and confirmed with a treponemic test, indicates immediate treatment in pregnant women and their partners. The congenital infection is preventable through adequate maternal treatment with benzathine penicillin, which presents great cost-benefit value. Toxoplasmosis is a parasitosis of worldwide distribution, with high prevalence in our environment. The serological screening during the prenatal period allows the detection of susceptible pregnant women who should be prioritized in educational activities and monitored for possible seroconversion. The early treatment of pregnant women with acute infection can reduce the maternal-fetal transmission or fetal impairment improving the prognosis of infected newborns. Syphilis and congenital toxoplasmosis can be avoided with a high quality prenatal, which should be available and accessible. Preventive and diagnostic actions should be intensified in the monitoring of pregnant women, especially in the basic health units (UBS), to generate population impacting results.

Key words: Obesidade; Gestantes; Saúde Pública; Saúde da Mulher.

RESUMO

*As infecções que acometem o binômio mãe-filho durante a gestação constituem grande preocupação para obstetras e pediatras, por sua frequência e dificuldade no diagnóstico etiológico, importante para o tratamento precoce. A maioria dos recém-nascidos com infecções congênitas é assintomática, assinalando a importância da triagem laboratorial para doenças transmissíveis durante o ciclo gravídico-puerperal da mulher. Este artigo de revisão visa a apresentar recomendações em relação às infecções congênitas por *Treponema pallidum* e *Toxoplasma gondii*. A sífilis é uma das doenças com maiores taxas de transmissão vertical e é um problema de saúde pública ainda com controle insuficiente no país. O diagnóstico da infecção materna, realizado com VDRL e confirmado com um teste treponêmico, indica tratamento imediato na gestante e em seu parceiro. A infecção congênita é prevenível por meio do tratamento materno adequado com penicilina benzatina, o que representa ótimo custo-benefício. A toxoplasmose é parasitose de distribuição mundial, com alta prevalência em nosso meio. O rastreamento sorológico durante o*

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pré-natal permite a detecção das gestantes suscetíveis que devem ser priorizadas nas ações educativas e monitoradas para identificar-se possível soroconversão. O tratamento precoce da gestante com infecção aguda pode reduzir a transmissão materno-fetal ou o comprometimento do feto, melhorando o prognóstico do recém-nascido infectado. É possível evitar a sífilis e a toxoplasmose congênita por meio do pré-natal de qualidade, que deve ser disponível e acessível. Ações preventivas e diagnósticas devem ser intensificadas no acompanhamento da gestante, principalmente nas unidades básicas de saúde (UBS), de forma a gerar resultados com impacto populacional.

Palavras-chave: Infectious Disease Transmission, Vertical; Congenital; Infant, Newborn; Toxoplasmosis, Congenital; Syphilis, Congenital.

INTRODUCTION

Changes have occurred in epidemiology, diagnosis, prevention, and approach to various infections. A review of the approach to neonatal vertical transmission of two infectious agents: *Treponema pallidum* and *Toxoplasma gondii* is proposed in this article.

METHODS

This was revision study based on the search of medical literature databases (National Library of Medicine – PubMed - MEDLINE; Latin American and Caribbean Center Literature on Health Sciences - LILACS; Scientific Electronic Library Online - SCIELO) in addition to publications by health organs (Center for Diseases Control and Prevention and the Ministry of Health). The following descriptors were used: congenital toxoplasmosis; congenital syphilis; vertical transmission of infectious disease.

Congenital syphilis

Epidemiology

T. pallidum still stands out as a public health problem and the prevention goal for 2015 is to reduce its incidence to 0.5 case per thousand live births.¹ In Brazil, despite the large access of pregnant women to prenatal care, availability of low-cost sensitive diagnostic tests, and effectiveness of treatment of pregnant women and fetus, children are still born infected. The reasons for

the high incidence of cases still observed relate to the lack in diagnostic tests according to the protocol recommended by the Ministry of Health and inappropriate conduct, such as absence of treatment of the partner.^{2,3}

Estimates from the Ministry of Health show that 1.1% of the Brazilian population becomes infected by *T. pallidum* every year and that about 60 thousand pregnant women (1.7%) are carriers of this infection, which is about four times higher the rates of HIV infection. According to the WHO, the mother-to-child transmission rate is of 25%. The occurrence of congenital syphilis is a clear indicator for the quality of health care in prenatal care, being under notified in our country.²

Since 1986, congenital syphilis is a mandatory notifiable disease for purposes of epidemiological surveillance.² In 2006, the disease was included as further notification in SINAN to facilitate the collection and analysis of records of cases in the country.⁴ According to the Ministry of Health, on the basis of the reported cases in 2008, 79.8% of the mothers had prenatal care. Of these, 52.9% had a diagnosis of syphilis during pregnancy, and only 23.7% had their partners treated (Table 1).⁵

In 2011, 9,374 new cases of congenital syphilis were reported, with the incidence rate of 3.3 cases per thousand live births.⁶ The incidence has increased and, in the country, regional differences in incidence rates and vertical transmission are detected, which shows the need for more effective measures to reduce this rate to acceptable levels. Table 2 presents the incidence over the years, stratified by region. Between 2005 and June of 2012, 57,700 notifications occurred in pregnant women, and 14,321 cases were in 2011 only; mostly in the Southeast and Northeast, with a detection rate of syphilis in pregnant women of 5.0 cases per 1,000 live births. Table 2 shows the national data of incidence of congenital syphilis in children aged less than one year. Rates of up to 3.3 per 1,000 live births in 2011 are recorded.⁶ However, it is estimated that underreporting can reach magnitudes of 44.2%.⁵

A total of 1,400 cases of congenital syphilis were notified in Minas Gerais in 2007 and 2008, with an incidence rate of 0.7 per 1,000 live births each year. In addition, 46 deaths were recorded for congenital syphilis in the State.⁷

Difficulties to control congenital syphilis and their incidence rate are also identified in developed countries, which had been declining in the US until 2006-07 and it started to rise again associated with the increase in the incidence of syphilis in the general population.⁸

Table 1 - Cases of congenital syphilis (%) by characteristics selected by diagnosis year – Brazil, 2001-2008

Diagnosis of congenital syphilis	2001	2002	2003	2004	2005	2006	2007	2008*
Pre-natal care performed	73,0	76,4	79,6	78,2	78,0	79,2	71,4	79,8
Syphilis diagnosed during pregnancy	53,1	58,4	57,1	56,4	56,3	55,1	57,4	52,9
Treated partner	17,5	18,8	17,9	13,7	13,2	13,1	20,1	23,7

Source: Brazil. Ministry of Health, Epidemiological Bulletin, DST/AIDS, 2008⁵.

Table 2 - Incidence of congenital syphilis in children less than one year old (per 1.000 live births) according to residence region by year of diagnosis, Brazil, 1998 to 2011

Region	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
North	0,3	0,4	0,6	0,8	0,7	1,7	1,2	1,6	2,0	2,4	2,3	2,2	2,1	2,6
Northeast	0,9	0,7	2,2	1,3	1,4	2,3	1,7	2,2	2,4	2,3	2,2	2,4	2,8	3,8
Southeast	1,1	1,3	0,6	0,6	0,6	0,6	2,2	2,2	1,9	2,0	2,1	2,2	2,7	3,6
South	0,5	0,6	1,3	1,2	1,1	1,6	0,7	0,8	0,8	1,1	1,1	1,5	1,8	2,5
Central West	1,2	2,0	1,4	1,4	1,1	1,3	1,5	1,6	1,6	1,2	1,4	1,4	1,6	1,8
Brazil	0,9	1,0	1,3	1,2	1,3	1,7	1,7	1,9	1,9	2,0	2,0	2,1	2,4	3,3

Source: Brazil. Ministry of Health, Epidemiological Bulletin, Syphilis, 2012.⁶

Definition

A pregnant woman is considered infected if during the prenatal period and at the time of delivery or curettage, clinical evidence of syphilis is detected with a positive test or without a test result.⁹

In addition, cases of fetal death by syphilis (all dead fetus, after 22 weeks of gestation or weighing equal or above 500 grams, whose mother is a carrier of syphilis and was untreated or inadequately treated) and abortion by syphilis (all gestational loss occurred before 22 weeks of gestation or weighing less than 500 grams, whose mother is a carrier of syphilis and was not treated or was inappropriately treated) must be notified.²

Congenital syphilis is considered in all children born to mothers with clinical and/or laboratory evidence for syphilis diagnosed during pregnancy, childbirth, or puerperium, and every child less than 13 years with clinical and/or epidemiologic suspicion.⁹

Vertical transmission

Congenital syphilis is the result of the spread of infection from pregnant women infected, untreated, or inadequately treated, to their fetuses through transplacental, peripartum, and even during breastfeeding if there are lesions in the breast. The rate of vertical transmission in untreated women is 70 to 100% in the primary and secondary phases of the disease,

reducing to approximately 30% in the late stages of maternal infection. More than 50% of reported cases are asymptomatic at birth, therefore, the serological screening of mothers during prenatal care and at the maternity is very important.^{2,3}

Clinical manifestations

Syphilis acquired during pregnancy can result in embryo resorption, miscarriage, stillbirth, malformation, CIUR, preterm birth, or postnatal varied sequelae such as blindness, deafness, mental disabilities, and malformations with early or late presentation.¹⁰

Early congenital syphilis manifestations, which occur up to two years of life, result from the action of treponema and are dependent on the bacterial load, virulence, fetal development at the time of infection, and the time elapsed between maternal infection and treatment. Among them are maculopapular rashes on the face, palmar, and plantar regions, bullous lesions, condyloma latum, osteochondrosis/ metaphysitis, syphilitic periostitis, osteomyelitis lesions, hemolytic anemia, hydropsia, retinitis in salt-and-pepper, chorioiditis, cataracts, and glaucoma.^{8,11}

The manifestations of late congenital syphilis, which occur after two years of life, result from inflammatory activity and bone remodeling. They include communicating hydrocephalus, periostitis and diaphysitis, tibia in sabre, olympic forehead, saddle nose, Hutchinson teeth, blackberry molars, short jaw,

high arched palate, interstitial keratitis, deafness by involvement of the 8th cranial pair, Clutton articulations, ragades, and cognitive deficit.^{8,11}

Diagnosis and treatment of pregnant women

A sure diagnosis is the identification of *Treponema pallidum* by dark-field microscopy. However, this examination is not frequently used due to technical difficulties in obtaining the material and in the exam performance.^{10,12}

The screening for syphilis with serological tests is justified by its high sensitivity, especially after the primary phase, and by a simple treatment available in the public network and with few side effects. In addition, the treatment still during gestation allows the treatment of the fetus and avoids evolution to lesions and congenital disease stigmas.^{2,3}

There are non-treponemal tests that are used for screening such as the Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR), which are treponemal tests used to confirm the diagnosis. The main treponemal tests used are the Fluorescent Treponemal Antibody (FTAAbs), *Treponema pallidum* haemagglutination assay (TPHA), and Enzyme Immunoassay (EIA). In primary syphilis, the sensitivity of the VDRL and FTAAbs tests reaches 75% and in the secondary phase of the disease both can reach 100% sensitivity. In the tertiary stage of syphilis, VDRL can be negative or present low titer regardless of treatment, but the treponemal tests remain positive.^{2,8} Still under investigation, the detection of *T. pallidum* DNA by polymerase chain reaction (PCR) stands out as a promising technique for prenatal and postnatal diagnosis allowing faster and more specificity in the identification of pathogens.⁸

Testing with VDRL must be initiated in the first prenatal consultation and repeated with 28 to 30 weeks, and in the maternity for all women in labor (Figure 1).¹³ It should be noted that any VDRL value should be considered for research and maternal treatment.² However, situations in which there may be false-positive serology must be remembered (leptospirosis, mononucleosis, vaccination, advanced age, leprosy, tuberculosis, malaria, lupus, neoplasms, injecting drug use, and own gestation) and false-negative (very recent syphilis, HIV associated, and prozone phenomenon – prevalence of antibodies over antigens).¹⁰

In addition, all pregnant women identified with syphilis should be notified and investigated for other sexually transmitted diseases (STDs). Although only VDRL and HIV serology are obligatory, according to the Program of

Humanization in the Prenatal and Birth¹³ and the Born Project¹⁴, the hepatitis testing must also be performed.

In December of 2011, the decree that defines the reverse screening with the treponemal rapid test and subsequent confirmation with the non-treponemal test or another treponemal test of different serological method was published.¹⁵ In October of 2012, the Ministry of Health published a technical note concerning the use of rapid tests in basic health units, allowing immediate treatment and avoiding missed opportunities in the treatment of syphilis, providing timely treatment to pregnant women and their partners.¹⁶

For the pregnant women, the treatment should be performed with penicillin in the appropriate dose according to the stage of the disease (Table 3).^{2,8}

In the case of neurosyphilis, crystalline penicillin is indicated (EV, 2 to 4 million IU every 4 hours) for 10 days. To be considered adequately treated, the pregnant women with a diagnosis of syphilis should receive penicillin in the appropriate dose, up to one month before delivery; the partner should be treated and the VDRL titer must be reduced at least four times in six months or remain less than 1:4 in the case of syphilis in unknown phase.⁸

Diagnosis and treatment of newborns

The conduct with newborns should consider if the mother was adequate or inadequately treated. The appropriate treatment depends on all the mentioned criteria, which must be met so that newborns do not require extensive propedeutics.²

If the mother is considered adequately treated, only VDRL performed simultaneously with the maternal test (paired) should be requested in the initial screening. If the VDRL is greater than that of the mother, or if the newborn is symptomatic, the propedeutics for investigation of target organs must be carried out for therapeutic decision in accordance with the alterations found. If the VDRL is equal to or less than the maternal values, the propedeutics should be performed if there is no possibility of follow-up. If the VDRL is negative, benzathine penicillin should be administered if there is adequate follow-up (Figure 2).²

If the mother is considered untreated or inadequately treated, the newborn must be subjected to entire propedeutics for investigation of target organs and therapeutic decision, regardless of symptoms, because 50% of them can be born asymptomatic (Figure 2).²

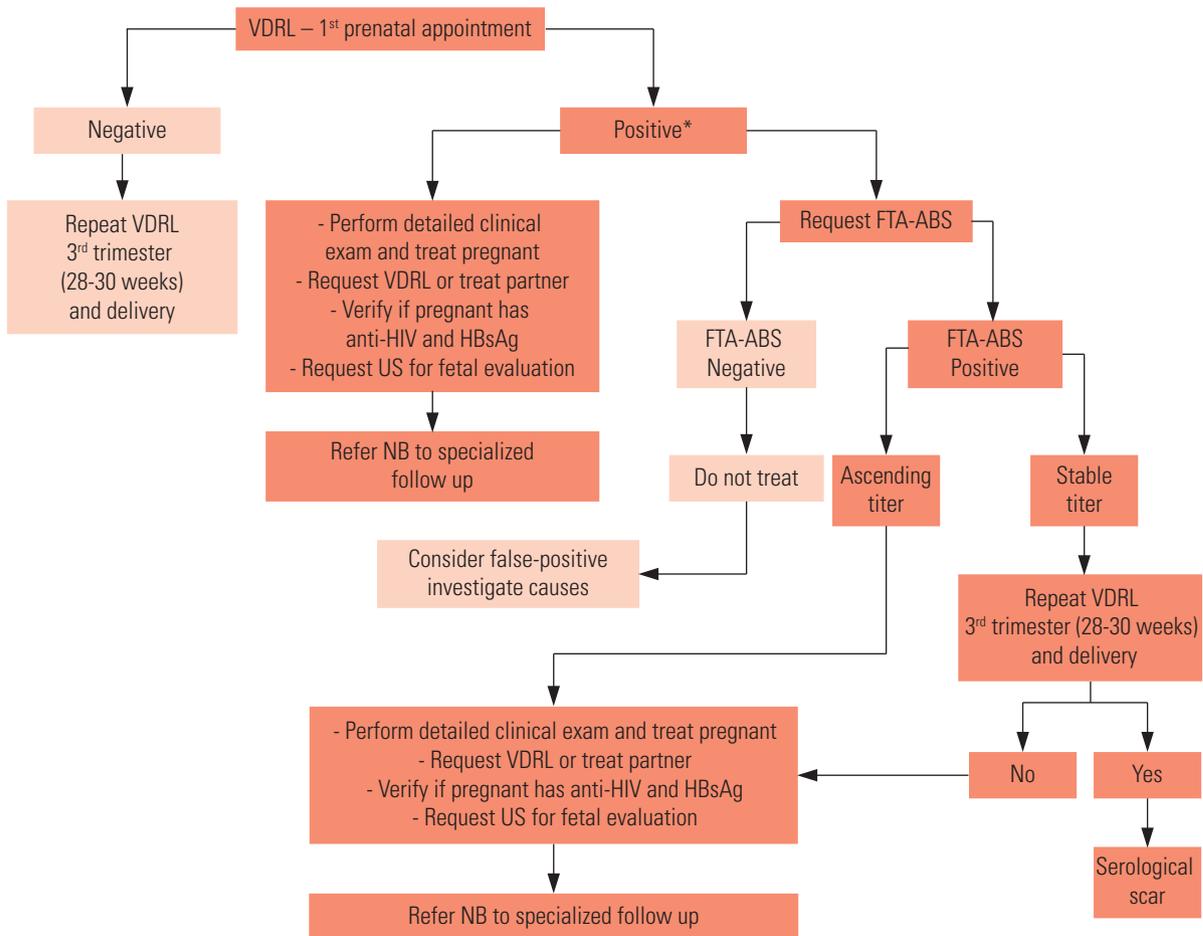


Figure 1 - Fluxogram for syphilis triage. Adapted from: Couto et al. (2006).¹⁰

* In the absence of a confirmatory test (FTA-ABS), consider pregnant women with reagent VDRL, at any titer for the diagnosis, if not adequately treated before.²

Table 3 - Treatment of syphilis during pregnancy and according to the disease phase

Syphilis stage	Treatment	Expected serological evolution
Primary (hard chancre)	Benzathine G Penicillin: 2.4 IU millions, IM, one dose	VDRL 4 fold drop in 3 to 6 months
Secondary or < 1 year	Benzathine G Penicillin: 2.4 IU millions, IM, two doses with one week interval	VDRL 4 fold drop in 3 to 6 months
> 1 year or unknown	Benzathine G Penicillin: 2.4 IU millions, IM, three doses with one week interval	VDRL ≤ 1:4, stable or decreasing

Source: Brazil. Ministry of Health, 2005.²

According to the classical references concerning the diagnosis of neurosyphilis, liquor alterations that suggest involvement of the central nervous system are: leucocytes above 25 cells/mm³ or proteins above 150 mg/dL (neonatal period) or leukocytes above 5 cells/mm³ and proteins above 40 mg/dL (after 28 days of life).² However, recent studies, conducted with more method-

ological rigor, have suggested lower values of cellularity, and mainly of proteins, as parameters of liquor normality in the neonatal period.^{17,20} Therefore, it can be prudent to consider the findings of cells and proteins in the liquor at levels lower than those classically accepted and correlate them with the child's clinic.

Follow-up after treatment

All children diagnosed with congenital syphilis, regardless of symptoms and infection site, should be evaluated and monitored by Infectious Diseases, Neurology, Ophthalmology, and Speech Therapy professionals.^{2,3}

Clinical followup should be conducted with monthly appointments for six months and later bimonthly, up to 12 months. VDRL must be requested at 1, 3, 6, 12, and 18 months to evaluate titer drops; two negative tests are needed for the ambulatory discharge.

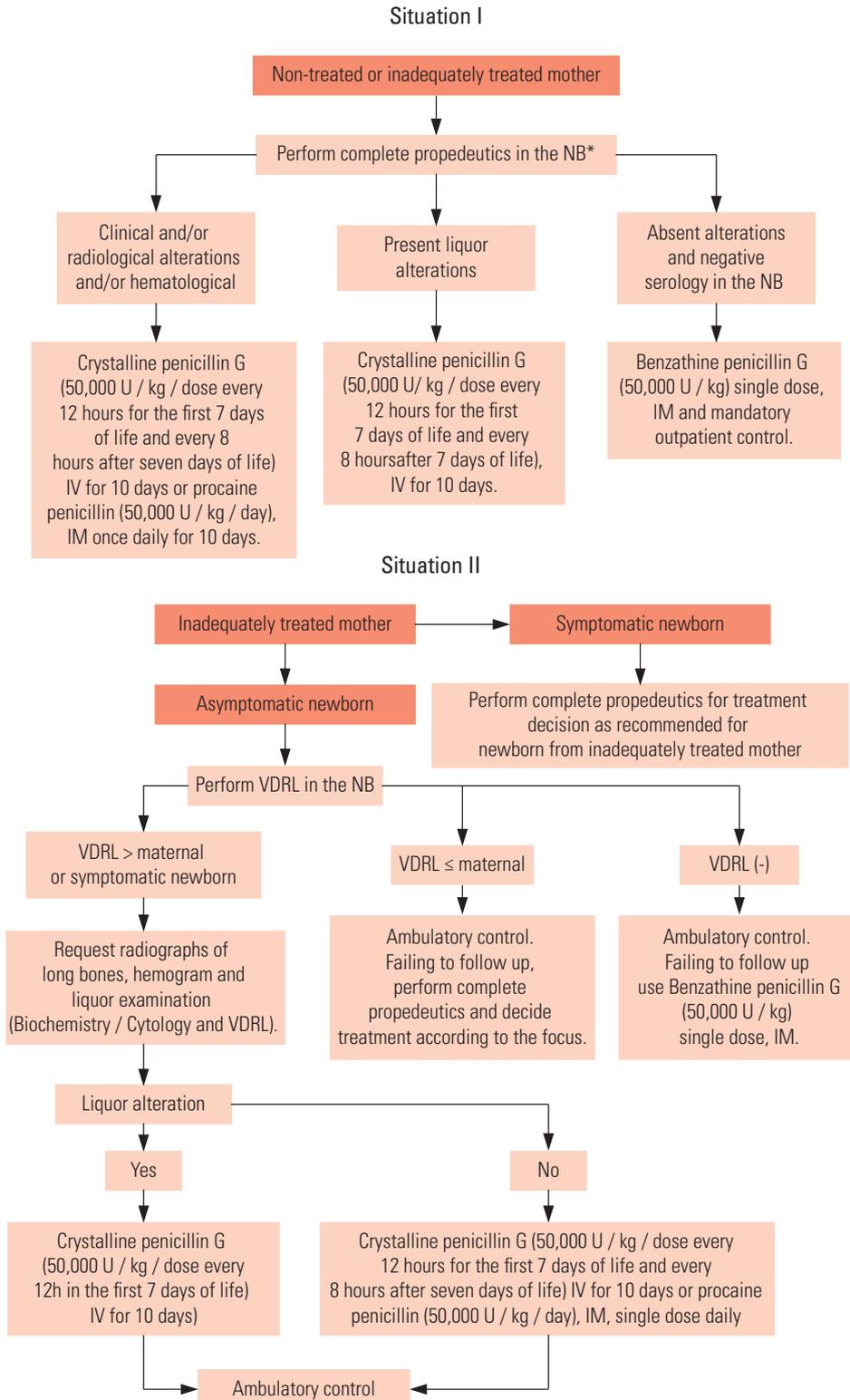


Figure 2 - Fluxogram for propedeutics and treatment of the newborn in case of syphilis in pregnancy according to maternal treatment.* The complete propedeutics includes: serum VDRL hemogram, liquor (biochemistry/cytology, VDRL) and radiography of long bones. It is highlighted that all cases definite congenital syphilis must be submitted to ophthalmological, neurological, and audiological evaluations. Funduscopy should be performed in all symptomatic newborn and other exams should be requested according to the newborn clinical status based on the target organs involved. Adapted from: Brazil, 2005.²

The child's FTAAbs should be requested after 18 months because their persistence indicate child's antibodies and confirms the diagnosis.^{2,3}

In cases of CNS involvement, liquor must be repeated every six months until normalization. The evidence of clinical and/or laboratory alterations in the child should be considered and as therapeutic failure or relapse and new evaluation should be performed for therapeutic definition.²

Congenital toxoplasmosis

Epidemiology

T. gondii is a cosmopolitan parasite with variable prevalence between regions according to certain characteristics such as eating and personal hygiene habits, sanitation, and socioeconomic status being higher in economically disadvantaged groups, as noted in underdeveloped countries.²¹ In the United States and Europe, a decline in prevalence has been observed in recent decades assigned, in part, to improvements in living conditions of the population.²²

Knowledge of the prevalence of congenital toxoplasmosis in general and in pregnant women is critical for the planning of rational public policies on the control of this disease. The impact of the disease in children infected in utero, and the number of susceptible women at risk of seroconversion during pregnancy should be considered in the evaluation of prevention strategies. Elevated prevalence indicates frequent environmental exposure, infection in younger age ranges, and high risk of seroconversion among susceptible pregnant women considering the contaminated environment in which they live.²³

In Brazil, studies evaluating the prevalence of toxoplasmosis in pregnant women show high rates, reaching 92% in Mato Grosso do Sul State.²⁴ In Belo

Horizonte, the evaluation in two public maternity wards detected a prevalence of 61.2%.²⁵

Estimates of congenital toxoplasmosis prevalences vary depending on the type of methodology employed and the region studied (Table 4). In Minas Gerais, a population-based study conducted between November of 2006 and May of 2007 encompassed all newborns participating in the State program of neonatal screening (PETN-MG), approximately 95% of live births in the period, and showed high prevalence of 13 infected for every 10,000 live births.²⁶

Despite the high frequency of congenital toxoplasmosis in Brazil, there are no public policies for infection control in the national territory. The Ministry of Health recommends serological screening at the first prenatal consultation and its repetition, when possible, transferring this decision and costs to the municipalities. Regionally, the prenatal screening is offered free of charge and with varied protocols in some municipalities of the States of Paraná, São Paulo, Minas Gerais, and Rio Grande do Sul.³⁰

Congenital toxoplasmosis prevention involves targeted measures to reduce the sources of infection and increase the general knowledge of the population about the forms of transmission and risks to the infected fetus. Thus, it includes policies related to improvement of health conditions and quality of water for consumption, care about the hygiene of animals reared for slaughter, appropriate processing of food, and women's access to quality preventive information during the prenatal period.³¹

Knowledge of risk factors by the population of pregnant women is essential for the educational strategy to succeed. It is known that infection occurs after ingesting one of the infective forms of *T. gondii* - cysts in raw or uncooked meat, sporulated oocysts in foods and water contaminated with cat feces, and rarely tachyzoites in raw milk. However, because there is variability among populations in relation to the importance of each risk factor, prophylactic guidelines must be adjusted to the reality of the target population.³²

Table 4 - Brazilian studies that evaluated the prevalence of toxoplasmosis using neonatal triage in dry blood

Author, year of publication and period of study	Site of origin	Sample	Prevalence (by 10.000)
Camargo Neto <i>et al.</i> , 2004 ²⁷	Brazil (non-specified areas)	364.130	5,3
Carvalho <i>et al.</i> , 2005 ²⁸ (2001)	Brazil (Ribeirão Preto)	15.172	3,3
Lago <i>et al.</i> , 2007 (2002) ²⁹	Brazil (Porto Alegre, RS)	10.000	6,0
Andrade <i>et al.</i> , 2008 (2003-2004) ²¹	Brazil (Belo Horizonte – MG)	30.808	6,5
Vasconcelos-Santos <i>et al.</i> , 2009 (2006-2007) ²⁶	Brazil (Minas Gerais)	146.307	13,0

The inclusion of acute toxoplasmosis and congenital toxoplasmosis in pregnancy in the “List of Mandatory Notification in Sentinel Units - LNCS” from the Ministry of Health in August 2010 was an advance in relation to the recognition of the importance of this disease.³³

The State Secretary of Health of Minas Gerais (SES-MG), considering the impact of the disease in our midst and the necessity for organizing the attention to diagnosis and treatment of toxoplasmosis, established the laboratory diagnosis in the Gestational and Congenital Acute Toxoplasmosis Network in pregnant women and newborns in MG since February 2013.³⁴ This action, called “Control of congenital toxoplasmosis program in Minas Gerais,” is conducted in partnership with the UFMG through the NUPAD (Center for Research and Action in support to Diagnosis). The program consists of performing triage in early prenatal care and repeated testing on a quarterly basis in susceptible pregnant women using the finger stick (blood on filter paper). IgM and IgG are investigated by the Elisa method. Pregnant women whose samples are IgM and IgG reagent on filter paper are retested in serum (IgM and IgG by the ELFA method) including the completion of the IgG avidity test. When the diagnosis of acute infection is confirmed or probable, the expectant mother is forwarded to the high-risk prenatal care, starts the use of anti-parasitic drugs and is evaluated for the diagnosis of fetal infection (PCR in the amniotic fluid). Children of pregnant women susceptible at the last examination carried out in the prenatal care and children of those with acute probable or confirmed infection are tested for IgM anti *T. gondii* (Elisa method) in blood collected for the neonatal screening triage. The infected child (IgM and/or IgA positive) is forwarded for treatment and rehabilitation if necessary.

With this new logistic system of toxoplasmosis diagnosis in the binomial mother-child, the profile of toxoplasmosis in Minas Gerais will become well known, which will provide more effective actions in preventing congenital toxoplasmosis.

Vertical transmission

Congenital infection occurs after transplacental transfer of *T. gondii* tachyzoites present in the circulation of the pregnant women with parasitemia mainly caused by acute infection. The transmission in pregnant women with chronic infection is uncommon;

however, it can occur in the situation of immunodeficiency associated with reactivation of latent infection or, more rarely, in immune-competent women who re-activated or were re-infected during pregnancy.³⁵

The rate of mother-to-child transmission is related, in a manner, directly proportional to the gestational age at which the maternal infection occurred: in the first trimester, during which the placenta presents low permeability, the transmission rate is low and around 6%. In the third trimester, the probability of congenital infection can reach over 80% due to the vast placental irrigation. The overall risk of toxoplasmosis transmission from mother to child during pregnancy was estimated at 29%.³⁶

Clinical manifestations

Congenital toxoplasmosis may be asymptomatic at birth or with variable clinical framework, which includes from nonspecific symptoms to serious manifestations with important sequelae or even abortion and fetal death. Clinical manifestations vary depending on factors such as the strain and parasite burden, immunity from the mother and child, and time of maternal-fetal transmission. The proportion of fetal impairment is presented inversely to the gestational age: the severity of congenital infection is greater in early maternal infections due to immaturity of the fetus, and smaller in infections that occurred at the end of the pregnancy. The classic triad of the disease – chorioretinitis, hydrocephalus, and intracranial calcifications – is seen in less than 10% of infected neonates. About 70-90% of children infected vertically present no symptoms at birth; however, they begin to show signs of the disease later in life due to auditive, central nervous system (CNS), and mainly ocular involvement. Out of all children who are born without any apparent symptoms, 40% or more features ophthalmological or CNS alterations when investigated. Among the unspecific manifestations are maculopapular rash, jaundice, hepatosplenomegaly, fever or hypothermia, lymphadenopathy, pneumonitis, diarrhea, anemia, and thrombocytopenia.³⁶

Retinochoroiditis is the most common manifestation, being predominantly bilateral and macular due to the parasite's predilection for the maculodiscal region. Other manifestations found in lesser frequency are microphthalmos and cataract. Strabismus and/or nystagmus suggest retinochoroiditis lesions.³⁶ Active

ocular lesion is characterized by a yellowish-white exudate, cottony and occasionally gray with ill-defined boundaries due to surrounding retinal edema.¹⁰

Neurological manifestations may be present at birth or appear between three and 12 months of life. They are more frequent in children with ocular involvement and can be caused by acute encephalitis or irreversible cerebral necrosis. The spectrum of alterations includes cerebral calcifications, microcephaly, hydrocephalus, and seizures. Hydrocephalus is usually progressive, hence the importance of cephalic growth monitoring. When it is secondary to the aqueductal obstruction, the literature reports good prognosis after ventricular derivation placement. Microcephaly is less frequent. However, it is associated with severe brain damage.³⁶ Contrary to microcephaly, calcifications have not been associated with learning disabilities.³⁷ Liquor alterations are characterized by hyperproteinorraquia and pleocytosis with mononuclear cells predominance.³⁶

Auditory deficit has been reported in less than 20% of cases of congenital toxoplasmosis, occurring to a lesser proportion in children with appropriate treatment; calcium deposition in the spiral ligament and cochlea is one of the mechanisms considered, similar to calcifications found in the brain.²¹

Diagnosis and treatment of pregnant women

Because only 10 to 20% of pregnant women with acute infections are symptomatic, serological screening is important in prenatal care to diagnose maternal acute infection (seroconversion). The first examination shall take place as soon as possible, ideally in the first trimester of pregnancy. The IgM and IgG anti *T. gondii* tests and the IgG antibodies avidity test are used to detect infection.^{10,36} It should be noted that pregnant women with initial susceptible serology (nonreactive IgM and IgG) followed by a positive IgG test may present chronic infection in which IgG was not detected in the first exam due to serological methods of low sensitivity or low levels of IgG. Figure 3 presents flowcharts that guide the interpretation of possible serological results and recommended conduct.

The method of choice for fetal propeudetics is the research of *T. gondii* DNA by polymerase chain reaction (PCR), which must be performed from 18 weeks of gestation and at least four weeks after the estimated date of maternal infection. The results should be

evaluated with caution in view of the wide variation in the performance of this diagnostic test between different laboratories. In general, the literature reports high specificity and variable sensitivity.³⁶

The treatment of pregnant women in the first trimester of pregnancy is performed with spiramycin and aims to decrease parasite transmission to the fetus. Pyrimethamine should not be used during the embryonic period because it is teratogenic in animals.³⁶

Because spiramycin does not reach therapeutic levels in the central nervous system of the fetus, with a positive PCR result in the amniotic fluid, it is advisable to exchange spiramycin by sulfadiazine associated with pyrimethamine, which must be maintained until the end of pregnancy. If the fetal infection is excluded, spiramycin treatment should be maintained until childbirth. If the primary infection occurs in the third trimester of pregnancy, it is suggested to start with sulfasalazine and pyrimethamine, due to the high risk of fetal contamination; amniocentesis is not required. Folinic acid must be used together with sulfadiazine and pyrimethamine to reduce the chance of medullary depression.³⁶

Diagnosis and treatment in the newborn

Considering that the clinical manifestations of infection are often absent in the newborn, the complementary examinations, especially the serologic, are very important.¹⁰

Congenital infection may be diagnosed through the isolation of *T. gondii* in the blood or bodily fluids; detection of the parasite's DNA by polymerase chain reaction (PCR); demonstration of cysts in the placenta and fetus and newborn tissues; or, more often, through serological tests.³⁶

The first RN serology should be performed simultaneously with the maternal serology. The best available techniques in Brazil for the detection of anti-toxoplasmosis IgM in neonates are the capture enzyme immunoassays (double-sandwich), which detect specific antibodies in approximately 80% of cases. Even using sensitive tests, many children infected before the 20th week of gestation will report negative results.^{21,36} A promising technique that can further assist in early diagnosis of congenital toxoplasmosis is the comparison of immunoglobulins IgG between child and mother through the "Western blot" technique that can identify different antigenic recognition profiles.³⁸

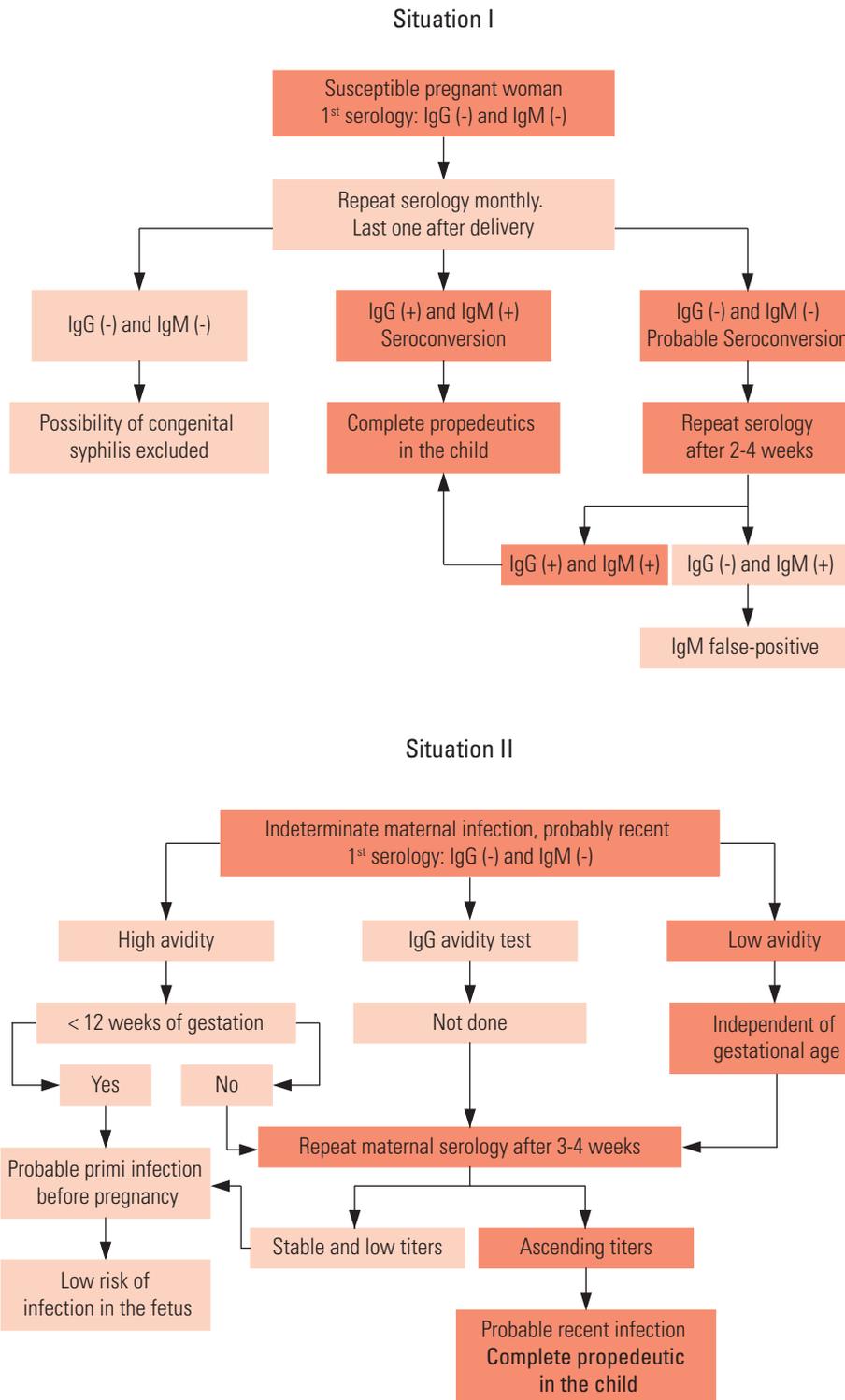


Figure 3 - Fluxogram for the interpretation of results from serology for toxoplasmosis performed during gestation.
 * Serological exams must ideally be performed in the same laboratory and using the same technique.
 ** The persistence of IgM positive antibodies after the interval of 2-4 weeks without the emergence of IgG antibodies suggests a false-positive result.
 Adapted from: Couto *et al.*¹⁰; SES-MG³⁴.

Anti-toxoplasmosis IgM antibodies can be detected two weeks after infection, reaching a peak of concentration within a month and becoming undetectable in about six to nine months. IgG antibodies reach peak concentrations in one to two months after infection and remain indefinitely positive. The finding of anti-toxoplasmosis IgG in the RN serum could mean active infection or passive transfer of maternal antibodies. Ascending IgG titers over successive controls are strongly suggestive of congenital infection, the same occurring with the persistence of titers in the first year of life. Conversely, the progressive fall of titers after the fourth month of life suggests passive transfer of maternal antibodies rather than fetal infection. In the absence of IgM, the isolated finding of anti-toxoplasmosis IgG in the asymptomatic RN serum does not confirm the diagnosis. However, if the RN presents clinical signs, the high IgG antibody titer has a high predictive value for the diagnosis of congenital toxoplasmosis. The propedeutics in the newborn should also consider the neurological, ophthalmic, and auditory evaluation. The performance of funduscopic examination is of the utmost importance because a portion of patients may be asymptomatic and present important ocular involvement. The presence of clinical manifestations at birth is usually associated with extensive retinal disease.^{10,21,36} The funduscopic examination should be performed by an experienced ophthalmologist, at birth and at regular intervals, in accordance with findings in the initial examination.

The neurological evaluation includes transfontanelar ultrasound (USTF), skull computed tomography (CT), and spinal tap. The USTF may show calcifications or hydrocephalus and is of great help in the diagnosis and monitoring of intra ventricular dilatation and extrauterine.¹⁰ The skull CT features more sensitivity to identify brain calcifications. The spinal tap is indicated in all cases with the clinical neurological alteration or in imaging tests.¹⁰ Alterations that are suggestive of neurological involvement are pleocytosis, usually less than 100 cells, with a predominance of mononuclear cells, and hyper proteinorria, which can reach high levels.³⁶

Auditory assessment should be conducted in all RNs with suspected congenital toxoplasmosis at birth. The procedures used for hearing assessment can be divided into behavioral assessments (subjective, with a high number of

false-negatives) and electrophysiological (objective, more sensitive and specific). The most used procedures among the electrophysiological ones are brainstem auditory evoked potentials (BAEPs)/brain stem evoked responses audiometry (BERA), and evoked otoacoustic emissions (EOAE). In the early hearing screening in children, performed during the first months of life, the use of the EOAE is recommended (popularized in Brazil under the name of hearing test). If altered, the BAEPs test is conducted.³⁹

Based on the findings in the approached clinical, serological, and complementary exams, the diagnosis of toxoplasmosis can be divided as follows:⁴⁰

Definitive diagnosis

- specific IgM (or IgA) in the first six months of age (the presence of these antibodies in the first five days of life needs to be confirmed with a new serology after the first week);
- specific IgG in elevation associated or not to clinical signs suggestive of congenital infection;
- specific IgG persistently positive at the end of the first 12 months of life associated or not to clinical signs that are suggestive of congenital infection.

Probable diagnosis

- positive placental tissue culture;
- specific IgM positive between 6-12 months of life, without a result from prior serology;
- specific IgG with titer equal to or less than the maternal titer, and may or not present liquor, fundoscopic, or radiological alterations suggestive of congenital infection associated with maternal infection confirmed during pregnancy.

Possible diagnosis

- retinochoroiditis and/or hydrocephalus/microcephaly/brain calcifications in children without serologic test results with unknown maternal infection;
- retinochoroiditis and/or hydrocephalus/cerebral calcifications in children with positive and specific IgG and unknown maternal infection.

Excluding diagnosis

- does not present detectable specific IgM and IgG in the first 12 months of life and did not receive treatment;
- negative serology (IgG and IgM) six months after the end of treatment.

It must be considered that IgG titers can be modified by treatment; therefore, it is necessary to confirm negative values between one and six months after the suspension of treatment.³⁶

All children with congenital toxoplasmosis, showing or not clinical manifestations at birth, should be treated during the first year of life, and the most widely used therapy is sulfasalazine, pyrimethamine, and folinic acid.³⁶

The sulfasalazine is recommended at the dose of 80 to 100 mg/kg/day in two shots a year. Pyrimethamine is used at the dose of 1 mg/kg daily for six months, and three times a week during the following six months. As the mechanism of action of these drugs involves the synthesis of folates that are essential for the metabolism of nucleic acids, the primary adverse event observed is the spinal cord reversible depression, represented mainly by neutropenia but also by macrocytic anemia and thrombocytopenia. To avoid this effect, folinic acid should be used at the dose of 5-20 mg/day three times a week or daily for infants, during and up to one week after suspension of the scheme.³⁶

Corticosteroids should be added to the anti-parasitic scheme in the presence of CNS inflammatory process (protein in liquor exceeding 1 g/dL) or eeti-nochoroiditis in activity near the macular region. The recommended dose of prednisone or prednisolone is 1 mg/kg/day in two takes until resolution of the mentioned alterations. In general, after 12 months of age no therapy is recommended, except in cases of reactivation of eye infection.³⁶

Follow-up after treatment

The child in treatment for congenital toxoplasmosis should be examined periodically by the pediatrician (weekly, monthly or bimonthly, depending on the evolution of the child). Growth and development must be followed up, referral to rehabilitation (low vision, physiotherapy, occupa-

tional therapy, and speech therapy) must proceed according to the needs of each child, and possible medicines side effects must be monitored.¹⁰

In suspected cases, the serology for toxoplasmosis (IgM and IgG) must be repeated at intervals of 1-2 months until confirmation or exclusion of the diagnosis. In infected children, the serology should be repeated at the end of treatment, when serological rebound can be observed with increasing levels of IgM and/or IgG. However, this isolated finding and without ocular inflammatory signs does not indicate the maintenance or resumption of anti-parasitic medication.³⁶

Infected children should be evaluated by an ophthalmologist at birth and then, ideally, every three months until one year of age, and every six months until isolated visual deficits can be reported.¹⁰

The neurological evaluation should occur at variable intervals according to the evolution of each case. In children with ventricular dilatation detected at the diagnosis, repeat USTF every two months and monitor growth of the cephalic perimeter strictly during the first year of life to assess the need of ventricular derivation.¹⁰

Auditory assessment should be performed in the neonatal period and during the first year of life.³⁹

The monitoring of adverse effects of medications used is also of great importance. CBC should be performed weekly at the beginning of treatment and can be repeated within longer intervals (1-2 months) in the absence of medications' side effects. If hematological alterations are observed, the dose and frequency of folinic acid use should double. The treatment should be suspended in the duration of severe neutropenia until the neutrophil recovery is up to levels above 500 cells/mm^{3,10,36}

Urinalysis is also recommended to monitor the occurrence of crystalluria, which can be avoided with simple guidance to increase water intake when using sulfasalazine.³

CONCLUSION

The importance of prevention and early diagnosis of toxoplasmosis and syphilis in pregnant women and newborns is emphasized, allowing the institution of appropriate treatment and improved quality of life for children.

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