

Serum IgG Titers Against *Toxoplasma gondii* in Uninfected Infants Exposed In Utero to Toxoplasmosis

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Objective: To describe the mean time of decrease of *T. gondii* IgG titers in uninfected infants exposed in utero to toxoplasmosis. **Methods:** A retrospective cohort study was conducted between 2008-2017, among infants under 12 months and exposed in utero to toxoplasmosis. Serial monthly monitoring of serum IgG titers were done till undetectable levels. **Results:** 240 infants with mean gestational age at diagnosis of 19.2 weeks were included in the study. The mean (range) time for IgG level to become undetectable was 7.9 (0.8-25.0) months. 14 infants became negative between 13-24 months. **Conclusion:** Majority of asymptomatic infants exposed in utero to *T. gondii* become seronegative before 12 months of age.

Keywords: Chorioretinitis, Intrauterine infection, Maternal exposure, TORCH.

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Toxoplasmosis is one of most prevalent infectious diseases in the World [1,2], with a prevalence of 60-80% in Brazil [3]. Approximately half of infected people are asymptomatic; however, infection during pregnancy can cause chorioretinitis and delayed psychomotor development in infants [4,5]. A congenital toxoplasmosis surveillance system was established in Brazil in 2016, which estimated rates between 0.3-1.3/1000 live births, one of the highest in the world [6,7].

Guidelines on management of infants exposed to toxoplasmosis in utero recommend screening paired blood samples from mother and baby and the target organs for disease at birth [8-10]. Infants are considered not infected if *Toxoplasma gondii* immunoglobulin IgM titers are negative and IgG titers are equal or lower than their mothers, with no evidence of congenital toxoplasmosis after complete clinical, radiologic, and laboratory evaluation. In these exposed infants monthly measurement of *T. gondii* IgG is recommended to exclude congenital infection. Levels of *T. gondii* IgG titers are expected to reduce by half every month until undetectable [2].

The follow-up of asymptomatic exposed infants can be time-consuming, and costly for health services and families. The aim of this study was to observe the time of decrease of *T. gondii* IgG titers of asymptomatic infants exposed in utero to toxoplasmosis.

METHODS

This retrospective cohort study was conducted at a reference pediatric infectious diseases center in a tertiary pediatric hospital, University of Rio de Janeiro, Brazil from 2008 to 2017. The study was approved by the institutional review board.

All infants up to 12 months of age referred with history of in utero exposure to *T. gondii* without infection at the end of follow-up were included. The study excluded subjects who were not followed up until the diagnostic definition, those who were referred after 12 months of life, those whose medical records were not available and those who were diagnosed with congenital toxoplasmosis during the follow up. The infant's vertical exposure to *T. gondii* was diagnosed by maternal acute infection during pregnancy defined by presence of serum IgM or reactive IgG for *T. gondii* in a woman with previously non-reactive IgG level. Additional criteria to define exposure without congenital toxoplasmosis were normal central nervous system (CNS) imaging by ultrasonography or tomography, normal fundoscopy, negative polymerase chain reaction test for *T. gondii* in amniotic fluid, negative *T. gondii* IgM, and undetectable IgG titers for *T. gondii* before one year of age [11]. IgA testing was not done as it was not available. The infant was considered as having congenital infection if any of these tests presented evidence of toxoplasmosis infection. The laboratory method used for the specific *T.*

gondii serology varied during the time of the study due to government supplies' availability. In most of them, the IgG was considered non-reactive if less than 1.0 IU/mL. Nevertheless, every time there was a change in methods, another serology was ordered for the children, as soon as possible, to make sure that the titers were decreasing.

Obstetric, clinical, demographic, and laboratory data were obtained from the medical records and collected in a standardized form. All data were included in a database using Access 2016 and analyses were performed using STATA software (version 13.0; Stata Corp LP) statistical program. Categorical and continuous variables were described by frequencies, central (mean and median) and dispersion measures (IQR). The time between birth and the first non-reactive *T. gondii* IgG sample was calculated and described in median (IQR).

RESULTS

In this study, 432 medical records of newborns and infants with a history of in utero exposure to toxoplasmosis were collected. The selection of the participants is shown in **Fig. 1**. A total of 240 exposed infants with mean gestational age 39 weeks, and mean birth weight and head circumference as 3231 g and 34.3 cm, respectively were included. The mean maternal age was 24.7 years and the mean gestational age at the time of maternal diagnosis of *T. gondii* infection was 19.2 weeks (35.5% in the first and 42.7% in the second trimester of pregnancy). Treatment with spiramycin or sulfadiazine and pyrimethamine was performed in 76.3% of mothers. Only 9 (3.7%) mothers reported any specific symptoms of toxoplasmosis, one had non-specific flu-like symptoms, 78 (32.5%) were asymptomatic (diagnosed through prenatal screening) and 152 (63.3%) did not have any information about the symptoms.

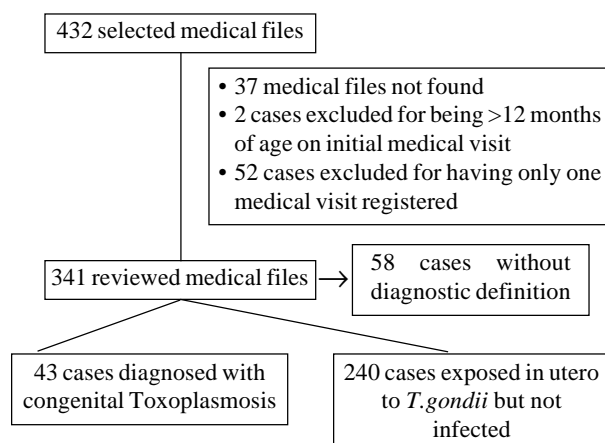


Fig. 1 Flow of the study.

The mean (range) time for toxoplasmosis IgG titers to become undetectable in the serum was 7.9 (0.8 to 25.0) months. The median (IQR) *T. gondii* IgG titers at the first visit were 115 (45, 223) U/mL. **Fig. 2** shows the time span to reach undetectable/ negative IgG titers in these patients, showing that 50% of uninfected infants took 7.3 (95% CI: 6.83-7.76) months to have a non-reactive serology. One infant had a positive IgM test after birth which was found to be non-reactive when tested after day five of life. The average age when the IgG levels became non-reactive did not change during the study period (data not shown).

Fourteen infants took more than 12 months (range 13 to 24 months), to present negative serology, 7 infants had a gap of more than 2 months between IgG titers measures near the 12 months mark. The remaining seven patients reached undetectable IgG titers between 14 to 19 months and remained asymptomatic throughout the follow-up, with normal target organ screening tests repeated a few times and a clear monthly drop in IgG titers.

DISCUSSION

In this study, we found that the mean age for IgG titer to become undetectable in newborn in utero exposed but not infected by *T. gondii* was 7.9 months.

A major limitation was missing data and medical records. The follow-up required frequent visits over a long period of time, which led some families to miss appointments or abandon the follow-up. The lack of standardized technique to perform *T. gondii* serology and change in laboratory techniques with time was another limitation.

The Brazilian guidelines recommend additional hematological and liver function tests in infants exposed in utero to *T. gondii* [9]. *T. gondii* IgG maternal antibodies passed to the newborn are expected to decrease by 50% each month until non-reactive between 6 and 12 months of

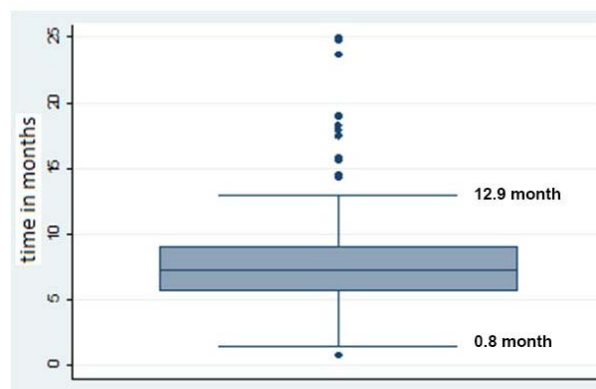


Fig. 2 Box-plot showing time span for toxoplasmosis IgG to reach undetectable levels.

WHAT THIS STUDY ADDS?

- Asymptomatic infants exposed in utero to toxoplasmosis may take longer than 12 months of age to achieve undetectable IgG titers.

life [2,12]. Therefore, a follow-up with monthly serological *T. gondii* tests until negativity of IgG is recommended [9,11]. Our results found a similar age range to reach undetectable specific IgG serology of 7.9 months.

In this study, the age for IgG titers to become undetectable ranged from 0.8 to 25.0 months unlike the range of 6 to 12 months described earlier [2]. Therefore, asymptomatic infants with low IgG titers should not be classified as infants with congenital toxoplasmosis at 12 months, and the presence of reactive IgG after 12 months as a diagnostic criterion for congenital toxoplasmosis should be re-evaluated. Asymptomatic infants with low IgG titers should be analyzed individually to serially monitor IgG decrease at 12 months of age. In such cases, patients may continue to be followed and be considered as only exposed in utero to toxoplasmosis but not infected when the serology is negative after 12 months of life.

Ethics clearance: IPPMG institutional review board; CAAE: 74564017.7.0000.5264, November, 2017.

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