



ORIGINAL ARTICLE

# Seroprevalence and vertical transmission of Chagas disease in a cohort of Latin-American pregnant women in a tertiary hospital in Madrid<sup>☆,☆☆</sup>



Laura Francisco-González<sup>a,\*</sup>, Teresa Gastañaga-Holguera<sup>b</sup>,  
Beatriz Jiménez Montero<sup>a</sup>, Zarife Daoud Pérez<sup>a</sup>, Marta Illán Ramos<sup>a</sup>,  
Paloma Merino Amador<sup>c</sup>, Miguel Ángel Herráiz Martínez<sup>b</sup>, José Tomás Ramos Amador<sup>a</sup>

<sup>a</sup> Department of Paediatrics, Hospital Clínico San Carlos, Madrid, Spain

<sup>b</sup> Department of Obstetrics and Gynaecology, Hospital Clínico San Carlos, Madrid, Spain

<sup>c</sup> Department of Clinical Microbiology, Hospital Clínico San Carlos, Madrid, Spain

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## KEYWORDS

Chagas disease;  
Vertical transmission;  
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## Abstract

**Background:** Chagas disease, caused by *Trypanosoma cruzi* (*T. cruzi*), is endemic in Latin-America and is emerging in Spain due to immigration. The vertical transmission rate is around 5%. A routine prenatal screening with serology of all pregnant women from endemic areas is recommended to identify infected newborns, allowing early treatment and cure.

**Objective:** The aim of this study was to estimate the prevalence of positive Chagas serology in a cohort of pregnant women from Latin-America and its vertical transmission.

**Patients and methods:** An observational, prospective, follow-up study was conducted on women with positive serology to *T. cruzi*, as well as their newborns, from January 2013 to April 2015. Congenital Chagas was ruled out using a PCR technique at birth and at 1 month, and with serology at 9–12 months old. A child was considered infected when PCR was positive, and uninfected when PCR was negative, and/or it had a negative serology.

**Results:** Screening was performed on 1.244 pregnant women from Latin-America, and there were positive results in 40 (prevalence 3.2%, 95% CI: 2.4–4.4%), with 85% of them from Bolivia.

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<sup>☆☆</sup> Previous presentations: this study was presented as a poster with discussion titled “Seroprevalencia y transmisión vertical de Enfermedad de Chagas en un hospital terciario de Madrid” at the VIII Congreso de la Sociedad Española de Infectología Pediátrica (SEIP); March 3–5, 2016; Valencia, Spain. Also as an electronic poster with discussion session titled “Vertical transmission of Chagas disease in a cohort of newborns in a tertiary hospital in Madrid” at the 34th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); May 10–14, 2016; Brighton, United Kingdom.

\* Corresponding author.

E-mail address: [Laura.francisco.gonzalez@gmail.com](mailto:Laura.francisco.gonzalez@gmail.com) (L. Francisco-González).

There was only one infected newborn (rate of vertical transmission 2.8% (95% CI: 0–15%)), who had a positive PCR at birth. Relative studies enabled an 8-year-old sister with an asymptomatic disease to be diagnosed and treated. Both were treated successfully with benznidazole (later the PCR and serology were negative).

**Conclusion:** Screening during pregnancy in Latin-American women helped to detect those with Chagas disease. The rate of vertical transmission was 2.8%, in keeping with literature. Screening led to the detection and treatment of previously unidentified familial cases.

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## PALABRAS CLAVE

Enfermedad de Chagas;  
Transmisión vertical;  
Cribado prenatal

## Seroprevalencia y transmisión vertical de enfermedad de Chagas en una cohorte de gestantes latinoamericanas en un hospital terciario de Madrid

### Resumen

**Introducción:** La enfermedad de Chagas, causada por *Trypanosoma cruzi* (*T. cruzi*), es endémica en Latinoamérica y emergente en España, ligada a inmigración. La transmisión vertical se estima de alrededor del 5%. Se recomienda cribado selectivo en el embarazo para identificar al recién nacido infectado, permitiendo tratamiento precoz y curación de la enfermedad.

**Objetivo:** El objetivo de este estudio fue estimar la prevalencia de serología positiva para *T. cruzi* en una cohorte de gestantes latinoamericanas y la tasa de transmisión vertical de la misma.

**Pacientes y métodos:** Estudio observacional prospectivo de gestantes con serología positiva para *T. cruzi* en hospital terciario, desde enero del 2013 hasta abril del 2015. El seguimiento de recién nacidos se realizó con PCR al nacimiento, repetida al mes, y serología a los 9-12 meses. Se consideró infectado al niño con PCR positiva y no infectado al niño con PCR negativa y/o negativización de anticuerpos.

**Resultados:** Se realizó cribado en 1.244 gestantes latinoamericanas, siendo positivas 40 (prevalencia 3,2%, IC del 95%: 2,4-4,4%), 85% procedentes de Bolivia. Solo un niño resultó infectado (transmisión vertical 2,8%, IC del 95%: 0-15%) con PCR positiva al nacimiento. La detección de la embarazada permitió estudiar a los hermanos, detectándose caso asintomático en paciente de 8 años. Ambos tratados con benznidazol con buena tolerancia, evolución favorable y negativización de PCR y anticuerpos.

**Conclusión:** El cribado de embarazadas latinoamericanas ha permitido la detección de gestantes con enfermedad de Chagas. La transmisión vertical fue del 2,3%, coincidente con la literatura. El cribado ha permitido la detección y el tratamiento de casos familiares no identificados previamente.

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## Introduction

Chagas disease, which is caused by the protozoan *Trypanosoma cruzi* (*T. cruzi*), is endemic in Central and South America (with the highest prevalence in Bolivia) and emerging in Spain and other European countries in association with the immigration of individuals from endemic areas to these countries.<sup>1,2</sup>

The main mode of transmission in endemic areas is vector-borne (triatomine bugs), but there are other routes of infection (ingestion of contaminated foods, blood transfusions, organ transplants and vertical transmission). Vertical transmission (whose prevalence is estimated at approximately 5% of newborns of infected mothers in endemic areas and 2–3% in non-endemic areas)<sup>3,4</sup> is the most frequent mode of transmission in Spain.

Selective screening of pregnant women is recommended for the subsequent identification of infected infants, which allows early treatment (better tolerated in the paediatric population) and cure of the disease.<sup>1</sup>

The aim of this study was to estimate the prevalence of positive serologic test results for Chagas disease in a cohort of Latin American pregnant women followed up in our hospital to establish the rate of vertical transmission.

## Patients and methods

We conducted a prospective observational study by following up a cohort of pregnant women with positive serological tests for *T. cruzi* and their newborns in a tertiary hospital in Madrid between January 2013 and April 2015.

Screening for Chagas disease (ELISA for *T. cruzi* [ARCHI-TECT Chagas Abbott]) was performed in all pregnant women from endemic areas (between Mexico and Argentina, with the exception of the Caribbean islands) in the first trimester of pregnancy. In women that tested positive, the result was confirmed by immunochromatography (SD BIOLINE rapid Chagas Ab test). Women with positive serologic test results were referred to the Tropical Medicine clinic for follow-up and treatment planning.

The follow-up of infants conformed to the consensus protocol of the Sociedad Española de Infectología Pediátrica, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica and Sociedad Española Ginecología y Obstetricia (Spanish Societies of Paediatric Infectious Disease, Infectious Disease and Clinical Microbiology, and Gynaecology and Obstetrics),<sup>5</sup> which call for performance of PCR at birth and 1 month of life, and serologic testing at birth and 9–12 months of life.

We considered infants with a confirmed PCR infected, and infants with 2 negative PCR results (at birth and at 4–8 weeks) or with a negative PCR and disappearance of previously detected antibodies not infected.

## Results

During the period under study, 1,244 pregnant women from Latin America (78% of the all pregnant women from this region) underwent screening for *T. cruzi*, of who 40 had positive results (prevalence, 3.2%; 95% confidence interval [CI], 2.4–4.4%). Of those with positive serologic test results, 85% were from Bolivia, 10% from Paraguay, 2.5% from Ecuador and 2.5% from Argentina. The prevalence in Bolivian pregnant women was 16.3% (95% CI, 12.6–20.8%).

We identified 40 infants born to mothers with positive test results for Chagas disease. Infection was confirmed at birth in only one infant (vertical transmission rate, 2.8%; 95% CI, 0–15%) born to a Bolivian mother aged 36 years with Chagas disease in the chronic indeterminate phase (asymptomatic). This infant had a case of symptomatic congenital Chagas disease (hydrops fetalis, ascites, haemodynamic instability, anaemia) and required admission to the neonatal intensive care unit. The patient had a positive PCR result at birth, and responded favourably to a 60-day course of treatment with benznidazole (initial dose of 5 mg/kg/day, raised to 8 mg/kg/day in the second week after ensuring absence of adverse events) that was well tolerated, with resolution of symptoms and negative results of a second PCR assay (at age 3 months) and serologic testing (at age 9 months).<sup>6</sup>

All the identified infants (with the exception of the case of vertical transmission) had negative PCR assays at birth and were followed up in adherence to the current protocol, with negative results of an additional PCR assay at 4 weeks and evidence of clearance of antibodies between 9 and 12 months. In our hospital, we did not perform microscopic examination of a blood smear at birth and age 1 month on account of its low sensitivity and the availability of PCR. In 75% of the infants (30), the follow-up was completed, with confirmation of absence of antibodies by serologic testing; in 87.5% (35) at least 2 PCR assays or 1 PCR assay and 1 serologic test at age 9–12 months were performed whose results were negative; while 12.5% patients (5) only had negative

results in an initial PCR assay at birth, and were therefore considered lost to follow-up.

The identification of infected pregnant women through positive serologic tests also allowed us to evaluate the siblings of their newborns, which led to the diagnosis of another asymptomatic case of Chagas disease in a girl aged 8 years (from Bolivia) that had not been detected at birth. She underwent treatment with benznidazole (at a dose of 10 mg/kg/day for 60 days) and was tested at regular intervals, tolerated the treatment well, and had a good outcome with eventual disappearance of antibodies (6 months after completing treatment). The remaining members of the household were evaluated at the Tropical Medicine clinic.

## Discussion

The selective screening of pregnant women from Latin America in our hospital allowed us to identify those who had Chagas disease, evincing a high prevalence among those from Bolivia.

The rate of vertical transmission in our cohort was 2.8% (95% CI, 0–15%), consistent with the data reported in the literature.<sup>3,4</sup> Few data have been published for non-endemic regions, but there is evidence of a lower rate of vertical transmission, which is probably due to pregnant women usually being in the chronic phase of disease, when parasite loads are lower.

Furthermore, screening of pregnant women allowed us to extend the evaluation to the rest of the household, with the detection and treatment of cases that had not been identified at birth. Thus, we were able to make an early diagnosis in paediatric cases, including cases in the asymptomatic phase, preventing complications and achieving cure of the disease.

Identification of infection in this cohort of pregnant women also allowed the follow-up of those infected, to whom we recommended starting treatment (if they had not already received it) once they stopped breastfeeding.

Vertically-transmitted congenital Chagas disease is usually asymptomatic (70–80% of cases). There is variability in the clinical presentation of patients who are symptomatic at birth, usually with involvement of several organs and systems,<sup>6,7</sup> as was the case of the sole case of vertical transmission identified in our cohort, which we have discussed in a previous publication.<sup>6</sup>

In newborns, a positive serologic test is no proof of infection, as it can also result from the placental transfer of maternal antibodies (IgG), so the diagnosis should be based on methods for parasite detection (PCR or blood smear examination), which we recommend performing at birth and repeating at age 1 month due to the possibility of false negative results (as their sensitivity depends on the level of parasitaemia).<sup>5</sup> In Spain, the use of PCR is recommended due to its higher sensitivity compared to blood smear (observation of the parasite by microscopic examination the smear). The sensitivity of PCR is high during the acute phase (up to 90–95%) and decreases during the chronic phase of disease (ranging between 50% and 80% in different case series)<sup>8,9</sup>; furthermore, it has a specificity of nearly 100%.<sup>8</sup> Nevertheless, microscopic examination of blood smears continues to be useful in endemic areas, where molecular techniques

such as PCR are less frequently available in laboratories, and its sensitivity depends on the experience of the individual performing the examination. While the yield of parasite detection methods is higher in children compared to adults because children are usually in the acute phase of disease and have higher parasite loads, confirmation of the disappearance of antibodies by serologic testing is recommended starting at age 9 months, although antibodies may not actually become undetectable until age 12 months. From age 9 months, the persistence of antibodies without a decrease in their titer is indicative of infection. In our cohort, serologic testing was performed between the ages of 9 and 12 months and was negative in all uninfected patients, who all had negative results in preceding PCR assays (we did not detect any false negatives of PCR). In children aged more than 12 months, as in adults, serologic testing is the gold standard for diagnosis, and positive results should be confirmed by performance of a different serologic test.<sup>5</sup>

When it comes to treatment, two drugs are currently authorised for Chagas disease: benznidazole (the treatment of choice) and nifurtimox (alternative treatment).<sup>10,11</sup> A paediatric formulation is not available for either. Clinicians should be aware that adverse reactions are less frequent and treatment is therefore better tolerated before age 7 years.<sup>12</sup> The data currently available do not suffice to determine the mechanism by which toxicity increases with age. It is believed that it involves increasing plasma concentrations of the drug, as the clearance rate is higher in children and results in a shorter half-life, which suggests that reducing the dose in adults to achieve concentrations similar to those found in children could reduce toxicity without affecting the effectiveness of treatment.<sup>13</sup>

The recommended dosage of benznidazole is 8–10 mg/kg/day administered in 2 doses for 60 days (it is the same for children and infants, except for preterm infants or patients with a concurrent disease in who a lower initial dose of 5 mg/kg/day is recommended, with increases starting 1 week after if the patient tolerates the drug well and laboratory tests results are normal until a dose of 8–10 mg/kg/day is reached).<sup>5</sup> The results of studies conducted in recent years in children as well as adults with Chagas disease in highly-endemic countries suggest that we should consider reducing the dose of benznidazole or the duration of treatment, as such reductions have not been associated with a decrease in efficacy.<sup>14,15</sup>

In the case of nifurtimox, which is usually prescribed in patients with poor tolerance of benznidazole, the recommended dosage is 15–20 mg/kg/day given in 4 doses for a period of 90 days.<sup>5</sup>

These drugs may cause adverse reactions, most frequently gastrointestinal, cutaneous and haematologic, which requires close monitoring of patients (including clinical manifestations and laboratory parameters) during treatment and the month following its completion.<sup>5</sup> In our study, none of the 2 paediatric patients treated with benznidazole experienced adverse events.

One of the limitations of our study is that due to the small sample size, the CI of the estimated vertical transmission rate was very wide. Performance of multicentre studies or studies with a longer period of follow-up would be advisable for the purpose of obtaining a larger sample size and thus more conclusive results. Furthermore, we could not

rule out vertical transmission in 5 patients who were lost to follow-up and who had a single negative result of PCR at birth. In one case, this was due to the death of the patient before the end of the study (due to disseminated tuberculosis), and in the rest, to patients not coming to the scheduled follow-up appointments. Since the population of interest is a population of immigrants, there are barriers to long-term follow-up, including the potential return to the country of origin.

To conclude, we ought to underscore that systematic screening of the at-risk population (pregnant women or children from endemic areas) is justified, as this disease has a silent course in a considerable percentage of patients (especially during the acute phase) and can be vertically transmitted, so that failure to perform screening may result in a delayed diagnosis. Based on our results, we believe that screening should be performed systematically in all patients coming from Bolivia, given the high prevalence of Chagas disease in this country, but also indicated in patients from any other Latin American country, among who cases also occur, in order to ensure early diagnosis and minimise the risk of complications.

Furthermore, treatment in newborns achieves a high cure rate (of nearly 100%) with a low associated toxicity, while the probability of adverse events increases and the probability of success decreases with the age of the patient.<sup>12</sup>

## Conflicts of interest

The authors have no conflicts of interest to declare.

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