

High Prevalence of Congenital *Trypanosoma cruzi* Infection and Family Clustering in Salta, Argentina

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ABSTRACT. *Objective.* *Trypanosoma cruzi*, the causative agent of Chagas' disease, is transmitted mainly by insect vectors, but congenital and transfusion-borne infections occasionally occur. The factors that are involved in transmission from mother to offspring are not well understood. The objective of this study was to study the presence of *T cruzi* infection in children who were born to infected mothers and in the children's siblings to evaluate the epidemiologic risk factors associated with congenital transmission of Chagas' disease.

Methods. Congenital *T cruzi* infection was studied in 340 children who were born to chronically infected mothers in Salta, Argentina. Infection was detected in 31 children, who were selected for additional study as infected index cases (IIC). Of the 309 noninfected children, 31 were taken as noninfected index cases (NIIC). We compared the prevalence of congenital *T cruzi* transmission in the remaining siblings of the IIC and NIIC. Data and blood samples were collected in house-to-house visits. Diagnosis of infection was established mainly by serologic methods, indirect hemagglutination, and enzyme-linked immunosorbent assay.

Results. The prevalence was 31.4% (32 of 102 children) for IIC siblings, whereas no infected siblings were found in families with NIIC (0 of 112). Clustering of congenital infection was found in 14 families, in which >1 child was infected. Second-generation congenital transmission (from grandmother to mother to newborn) was established in 4 families. The association among low weight at birth, prematurity, and congenital transmission was highly significant. An important observation was the absence of pathologic findings in a high proportion of infected children. The detection of asymptomatic infections was a consequence of population screening, as opposed to hospital-based diagnosis, for which symptomatic cases predominate. Congenital transmission was associated with the geographic origin of mothers: women from areas where insect vectors proliferate were less likely to give birth to infected offspring than women from areas under active vector control.

Conclusions. Siblings of an infant infected with *T cruzi* are at high risk for infection themselves and, even in the absence of symptoms, should also be screened for infection. The findings of family clustering of infection and of second-generation congenital infection in vector-free areas suggest that new modalities of transmission,

other than classic vector-borne spread, may occur both in endemic and in nonendemic areas. *Pediatrics* 2005; 115:e668–e672. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1732; *Trypanosoma cruzi*, Chagas' disease, family clustering, congenital infection.

ABBREVIATIONS. IC, index case; IIC, infected index case; NIIC, noninfected index case; Ag, antigen.

Chagas' disease (American trypanosomiasis) is a parasitic disease with considerable impact on public health. The main factor associated with transmission is the presence of triatomine insect vectors in human houses, so Chagas' disease is most commonly associated with poor, rural dwellings. Vector control with insecticides has been successful to reduce the global seroprevalence in some countries.¹ In the province of Salta, Argentina, the proportion of seropositive, 20-year-old soldiers dropped significantly during the 1980s.²

Socioeconomic factors that have prevailed in Latin America in the past 3 decades have produced large-scale migrations from rural to periurban settlements. This has given rise to the epidemiologic phenomenon of "urbanization of parasitism," meaning that Chagas' disease is no longer found exclusively in the rural environment. As a consequence, new transmission modalities such as congenital and transfusional are occurring in the absence of insect vectors. A previous study in northwestern Argentina³ revealed that in 8.8% of the deliveries from *Trypanosoma cruzi*-infected mothers, congenital transmission occurs.

Congenital *T cruzi* infection seems to be, on the basis of hospital records of clinically detected cases, a symptomatic condition that presents with fever, edema, lymphadenopathy, anemia, hepatosplenomegaly, and cardiomegaly.^{4,5} However, the true frequency of asymptomatic cases should be examined by active search studies, such as the present one. The standard diagnostic methods are the microhematocrit,⁶ which allows detection of parasites in blood during the first months after birth, and the serologic reactions.⁷ Indirect hemagglutination and enzyme-linked immunosorbent assay should be applied after the eighth month of age to avoid detection of passively acquired antibody. Treatment with 5 mg/kg per day benznidazole for 2 months is most often successful, as indicated by the progressive decline of antibody. Early detection and treatment become a relevant issue of public health, considering that early drug treatment is curative^{8–12} and up to 30% of in-

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fect, nontreated children irreversibly progress toward the chronic phase of Chagas' disease.^{4,13}

Risk factors for congenital *T. cruzi* infection are poorly understood.¹⁴ No clear association of this mode of transmission with factors such as maternal age, number of previous deliveries, or geographic origin has been found.¹⁵ Most epidemiologic studies on congenital transmission simply state the number of studied cases and the number of positive diagnoses found, without analyzing their association with epidemiologic factors in mothers and newborns. Several reports have documented the transmission of *T. cruzi* from one mother to 2^{4,5,13,16} or several^{17,18} of her offspring, whereas other siblings are spared from infection.¹⁷⁻¹⁹ At least 2 cases of second-generation congenital infection have been published.^{13,20} The purpose of this work was to study the presence of *T. cruzi* infection in children who were born to infected mothers and to evaluate epidemiologic risk factors associated with congenital transmission of Chagas' disease.

METHODS

Study Area

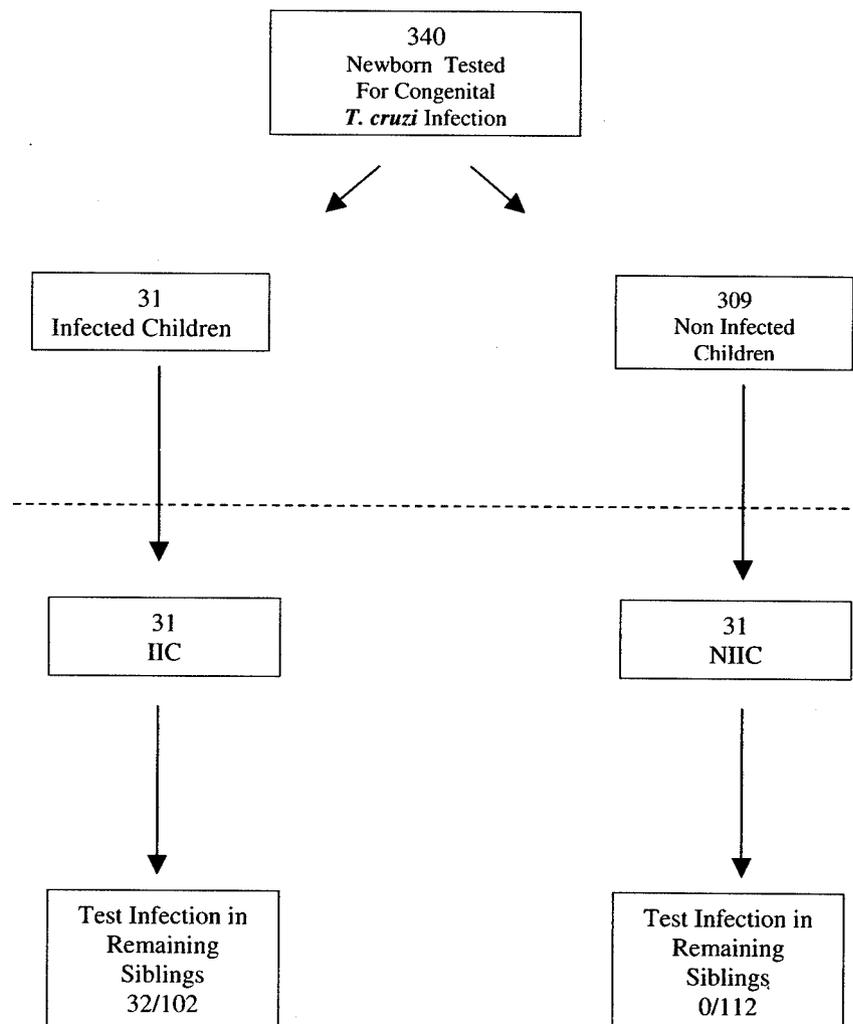
This study was conducted in the northern Argentina city of Salta, located in a sub-Andean valley 1220 m above sea level, with 462 668 inhabitants. Several large settlements have added 108 100

new habitants to the metropolitan area in the past 10 years. This new population consists largely of migrant families from rural areas, which are endemic for Chagas' disease. Triatomine vectors were eradicated from Salta city in the 1970s, and no reinfestations have been registered in the areas where this study was performed.

Selection of Study Groups

In the province of Salta, serologic detection of *T. cruzi* infection is mandatory for pregnant women. In public health centers, compliance with this regulation allows the detection of a few dozen infected pregnant women every month. Between July 1997 and January 2002, a collaborative project to improve diagnostic methods was undertaken by some public maternity hospitals (listed in the Acknowledgments) and our laboratory. This provided an initial survey of 340 infants who were born to *T. cruzi*-infected mothers and subjected to serologic or parasitologic search for *T. cruzi* infection. From this original population, index cases, with or without congenital infection, were selected for the studies reported in this article (Fig 1). Index case (IC) is defined here as the first child studied in a family in which all available, remaining siblings are later subjected to the same study. All 31 infants who tested positive were termed the infected ICs (IICs). We identified and studied the 102 remaining siblings in the 31 families of these IICs who resided in the study area. Conversely, 31 noninfected children from the original group of 340 were selected as noninfected ICs (NIICs), and we identified 112 remaining siblings in the 31 families with residence in the area studied. NIICs were selected when they had siblings, lived in Salta city, and were available for follow-up. The age at testing did not differ significantly between IICs (2.4 ± 2.7 years) and NIICs (1.2 ± 0.6 years). Regarding the siblings of IC, their age at the time of testing was 6.5 ± 4.8 for IIC siblings and 7.7 ± 4.4 for NIIC siblings. *T. cruzi* infections were

Fig 1. Selection of study groups.



considered "congenital" only when transfusions or travel to areas of vectorial transmission were excluded.²¹

Data Collection

Data and blood samples were collected in house-to-house visits. The following items were obtained from every family: place where mother was born and grew up; number of children; mother's age at each delivery; most probable route of mother's infection (vector, transfusion, congenital, or not determined); child's gender, weight at birth, gestational age, and birth date; and child's history of infections, transfusions, and travel to endemic areas during the first year of age. Data from basic clinical laboratory tests (hemogram, liver function tests) were added to the clinical record of most children.

Serologic Determinations

Blood was collected by venous puncture, and serum was separated.

Indirect Hemmagglutination

Serial serum dilutions were mixed with red blood cells that were sensitized with cytoplasmic *T. cruzi* antigens. The specifications of a commercial kit (HAI-Wiener, Rosario de Santa Fé, Argentina) were followed. Samples that agglutinated at dilutions of $\geq 1/16$ were considered positive.

Enzyme-Linked Immunosorbent Assay

A kit (Chagatest-Wiener, Santa Fé, Argentina) that included 2 types of antigens (Ags) was used (a crude, cytoplasmic, and membrane Ag and recombinant Ags). These included the shed acute-phase Ag; reactive during the acute stage, the recombinant 1, 2, and 30 Ags, reactive during the chronic stage; and the 13 and 36 Ags, reactive during both acute and chronic stages of Chagas' disease.²²⁻²⁴ Because all children who are born to infected mothers display passively transferred antibodies from their mother for several months,^{4,5} we referred to children as "seropositive" only when the positive reactions were obtained after 8 months of age and were confirmed in the same subject after ~12 months of age.

Statistical Analysis

Means and SDs are expressed as $x \pm SD$. In bivariate analysis, the significance of differences in proportions was analyzed with the Fisher exact test, the χ^2 test, and Pearson correlation.²⁵ For multivariate studies, Wright coefficients in Path analysis were used.²⁶ Analysis of clustering was made by comparing observed with expected cases on the basis of a Poisson distribution.²⁷

RESULTS

Families With and Without Infection

Between July 1997 and January 2002, 62 families in which the mother was seropositive and asymptomatic were studied. In 31 families with an IIC, 32 (31.4%) of the 102 remaining children were seropositive 8 or more months after birth. The 95% confidence interval for proportion of seropositivity in these remaining children was 0.2237 to 0.4037. In the 31 families with an NIIC, no seropositivity was found in the remaining children (0 of 112; $P < 10^{-6}$; Fig 1).

Family Clustering

This analysis was performed on the 31 families (133 children) with an IIC (Fig 1). In 14 of these families, >1 infected child was found. The theoretical probability of this event was 1.11×10^{-16} , on the basis of random Poisson distribution (with $\lambda = .22$). Thus, the finding of second and additional infected children in a family was not a randomly distributed event but clustered in particular families.

Clinical-Obstetric Data of Infected Mothers

All deliveries were normal, and only 5 mothers presented mild complications during pregnancy. Frequency of abortions did not differ ($P = .39$) between families with and without infected children.

Effect of Mother's Stage and Route of Infection on the Infection Status of Her Offspring

The history of the mother's stage (acute or chronic) and possible infection route (vector, congenital, transfusion, or not determined) were investigated in all 340 cases. Although data were inconclusive for many mothers, conclusive evidence for a particular stage or route of infection was obtained in 40 mothers for vector-delivered infection, the vectorial route, in 6 for congenital infection, and in 1 mother for the transfusion-delivered infection.

Vectorial Infection

Twenty of the 40 mothers who were infected by insect vectors gave birth to infected children. The number of children who were infected in this group was 41 of 188 studied in this group.

Second-Generation Congenital Transmission

Four of the 6 congenitally infected mothers gave birth, in turn, to 13 infected children of a total of 26 children studied.

Acute, Transfusional Infection

Three of the 4 children from the transfusionally infected mother were also infected, either during or after her acute stage.

Geographic Origin

In 62 of the mothers whose children were analyzed in this study, a distinction could be established regarding their place of origin, in terms of contact risk with insect vectors of *T. cruzi*: (1) 18 mothers came from high-risk departments of Bolivia, a country with very scarce vector-control activities and high rates of seroprevalence; (2) 26 mothers came from the Chaco region of Salta, where risk of contact with vectors has been high, but vector-control activities have increased in the past 2 decades; and (3) 18 mothers came from places in Salta and other provinces where the risk of contact with vectors is low. The proportion of families with infected children in each of these groups was analyzed. A correlation between high-endemicity, Bolivian (33%), vector-controlled (50%) and low-endemicity (66%) areas of origin was apparent. The differences between extreme groups (low endemicity vs Bolivian) was significant at the $P = .045$ level (Table 1).

Relationship Among Birth Weight, Gestational Age, and Congenital Infection

This association was analyzed in 300 of the 340 children of the initial survey (Fig 1, top box). They were divided in 2 groups, according to gestational age—premature (30–37 weeks of gestation) and mature (38–40 weeks of gestation)—and the rates of congenital transmission were determined for both

TABLE 1. Proportion of Congenitally Infected Children Who Were Born to Mothers From Different Regions of Origin

Mother Origin	Congenital Infection in Family, n/N (%)	P*	Infected Children, n/N (%)
Bolivia	6/18 (33)	0.045	8/80 (10)
Chaco	13/26 (50)	0.27	27/129 (21)
Low-endemicity areas	12/18 (66)	—	28/67 (42)
Total		—	63/276 (22)

The lower rate of congenital transmission in high-endemicity as compared with low-endemicity areas is apparent in both families (second column) and individual children (fourth column). However, statistics are applied to families and not to individual children, because “within-family” measurements strongly depend on each other.

* P value as compared with low-endemicity areas; calculated by χ^2 test.

groups (Table 2). A very high infection rate (50.0%) was detected in premature children who were born to *T. cruzi*-infected mothers. In mature children, the proportion was 8.7% ($P = 4.1 \times 10^{-6}$). The trivariate Path analysis indicated that the correlation between birth weight and infection is significant ($r = -0.10$; $P = .016$) and is strongly determined ($r = 0.55$) by the correlation between birth weight and gestational age ($r = 0.55$; $P < .0001$). In Fig 2, the rates of infection in different categories of birth weight are depicted, showing that at lower birth weights, higher rates of infection are observed. Even after excluding premature children, the association of weight at birth and congenital *T. cruzi* transmission was still highly significant. Thus, low birth weight and prematurity, independently of each other, should be taken as possible signs of fetal infection with *T. cruzi*.

Other Correlations

No influence on the proportion of congenitally infected children was detected regarding mother's age of delivery, gender of the child, or sibling order.

Pathology of Congenitally Infected Children

For this analysis, every infected child ($N = 63$; 31 IIC + 32 infected siblings) was matched to 1 of his or her noninfected brother or sister who differed in age by <5 years. Table 3 displays the association of several pathologic-clinical findings at birth with congenital infection. Most anemic children (16 of 18 [89%]) were infected. A few cases of hepatomegaly, cardiopathy, pneumonia, and adenopathy were found in the study group. These were present only in *T. cruzi*-infected subjects. It was remarkable that 53.9% (34 of 63) of the infected children in this study did not present pathologic findings and that jaundice was equally distributed among those with and without infection.

DISCUSSION

Because the area where this study was conducted is free from triatomine vectors, it is assumed that *T.*

TABLE 2. Relationship Between Gestational Age and Rates of Congenital Transmission

Gestational Age, mo (wk)	Infected/Total	%	P*
7-8 (30-37)	6/12	50.0	4.1×10^{-6}
9 (38-40)	25/288	8.7	4.1×10^{-6}

* Fisher's exact test.

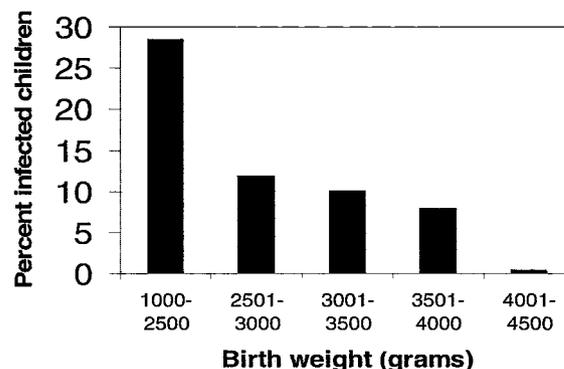


Fig 2. Rates of congenital *T. cruzi* infection by birth weight of newborns of infected mothers.

TABLE 3. Main Clinical Findings in *T. cruzi*-Infected Children

	Infected	Noninfected	Total
No signs	34	56	90
Jaundice	6	5	11
Anemia	16	2	18
Hepatomegaly	1	0	1
Cardiopathy	1	0	1
Pneumonia	4	0	4
Adenopathy	1	0	1
Total	63	63	126

cruzi infection that was detected in these children has been transmitted congenitally. The main points from this work that are important in terms of changing the approach to screening for congenital Chagas' disease are as follows. (1) Asymptomatic women transmit *T. cruzi* almost 10% of the time (31 of 340). Therefore, all pregnant women in endemic areas should be screened and infants of seropositive women should also be screened. (2) Detection of an infected infant identifies siblings who are at high risk, so the siblings should be screened. (3) Symptoms may be absent or mild. If universal coverage cannot be adopted, then screening should at least be applied to infants with prematurity, low birth weight (even in the absence of prematurity), adenopathy, hepatosplenomegaly, or anemia.

In this study, when the mother was infected and her child was spared from infection, no complications during pregnancy and delivery were apparent. However, when the child was infected, premature delivery and low birth weight were very frequently associated. Another salient finding of this study was the apparent absence of pathology in most infected

children. This may be explained by the modality of case recruitment used here. Whereas most studies^{5,13,19–21,28} are based on recruitment of symptomatic individuals who seek medical attention, this study was based on a house-to-house, serologic screening for infected children. Most individuals so identified were asymptomatic or had only mild symptoms.

The finding of *T. cruzi* transmission clusters in vector-free areas indicates that in recent years, the modes of transmission of Chagas' disease have been changing. These changes have important implications for the control of the infection. Insect control campaigns have been successful in the past 2 decades, substantially interrupting vectorial transmission in rural and urban environments of the province of Salta.²¹ Our present observation of infected children in rapidly growing, vector-free suburban neighborhoods of the capital city indicate that congenital transmission is becoming increasingly responsible for the urbanization of the disease. Urban transmission circuits of *T. cruzi* may be enriched in parasite lineages adapted to transmission modalities that are less dependent on vectors, such as placental passage. This hypothesis would be consistent with our finding that infected mothers from low-endemicity areas tend to transmit *T. cruzi* more often to their newborn than mothers from areas of high vector infestation, such as Bolivia.

Serologic monitoring of all deliveries from *T. cruzi*-infected mothers, estimated at 4.5×10^3 per year in the province of Salta, represents a considerable burden for public health services. Complete coverage is rarely achieved. However, not all newborns of infected mothers may be at the same risk level. We have indeed shown that the occurrence of a previous congenital case in the same family of a premature or underweight newborn or the presence of hypochromic anemia is associated with high risk. The notion, supported by this study, that high-risk subgroups may be identified easily allows the concentration of diagnostic resources in smaller populations that are much more prone to the event of congenital transmission.

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