Supplement Article

Mother-to-Child Transmission of *Trypanosoma cruzi*

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Among the world's most neglected tropical diseases, Chagas disease is vector-borne and caused by *Trypanosoma cruzi*. *T cruzi* infection is endemic to South and Central America as well as Mexico. Due to population migration, *T cruzi* is increasingly becoming a public health problem in nonendemic settings. Success with vector control strategies has led to a relative increase in the burden attributable to congenital transmission of *T cruzi*. In endemic settings, approximately 5% of infected pregnant women transmit to their offspring. Congenital *T cruzi* infection is generally asymptomatic and parasitological and serological testing is required for diagnosis. This review highlights research gaps with a focus on (1) improving screening, diagnostic, and treatment options and (2) designing epidemiologic studies to understand risk factors for congenital *T cruzi*.

Key words. Chagas disease; congenital infection; research gaps; *Trypanosoma cruzi*.

Chagas disease (American trypanosomiasis), a vector-borne disease caused by *Trypanosoma cruzi*, is among the world's most neglected tropical diseases [1]. An estimated 10 million people are infected with *T cruzi* globally, mostly in Latin America [2]. Approximately 11 000 deaths were attributed to complications of Chagas disease in 2008 [2]. Acute *T cruzi* infection is associated with high parasitemia and is generally asymptomatic. Approximately 20%–30% of those with *T cruzi* infection later develop Chagas disease, a chronic condition marked by low or undetectable parasitemia and clinical symptoms, including cardiovascular and or digestive conditions [2].

The cause of the disease and the insects responsible for transmission were discovered in 1909 by Brazilian physician Carlos Chagas. He found that domesticated insects associated with poor quality housing were the vectors of *T cruzi*. The most significant vector in South America is *Triatoma infestans* [3, 4]. Triatomines become infected with *T cruzi* parasites when they take blood meals from infected animals or humans. Infected triatomines can then infect other animals and humans on future blood meals. They deposit feces containing parasites near the bite wound, which later results in human infection.

Tremendous advances have been made in vector control in parts of Latin America. *Triatoma infestans* has been eradicated from Brazil, Chile, and Uruguay and elimination is in progress in other areas [4]. In addition to vector transmission, *T cruzi* can also be transmitted through other routes including blood transfusion, organ transplant, oral transmission, and transplacental transmission. Control of blood supply sources for *T cruzi* infection has been rigorously addressed in many countries [3]. The success with vector control has led to a relative increase in the burden attributed to congenital transmission of *T cruzi* [5–8]. This review will highlight gaps in the literature and focus on diagnosis, clinical features, prevention, treatment, epidemiology, and pathophysiology of mother-to-child transmission (MTCT) of *T cruzi*.

Diagnosis

One of the major challenges for controlling congenital *T cruzi* is the availability of valid and reproducible screening and diagnostic tools. Rapid tests have been developed and are performed to assess *T cruzi* infection in mothers and children. The results are used to identify infants at risk of congenital infection [9]. However, concordance between different rapid tests has been low in some countries, and there is a need to develop new valid and reproducible tests [6]. Diagnostic protocols require use of 2 or more

different tests and a lengthy follow-up schedule for appropriate and complete examination of infants born to infected mothers [2]. Direct parasitological examinations are performed on cord blood or on blood samples obtained by heel prick during the first weeks of life. When parasitological examination is negative, infants are followed up and serological examinations are performed after 8 months of life, when maternal antibodies have disappeared. This strategy is a major challenge in the field: direct parasitological examinations require trained personnel and have a low sensitivity, and loss to follow-up often precludes serological examinations after 8 months. Polymerase chain reaction molecular techniques have also been used along with other serological and or parasitological assays to diagnose congenital *T cruzi* [10–12].

Clinical Features

In most cases, congenital *T cruzi* infection is asymptomatic at birth but carries a risk of cardiac disease and other complications of chronic Chagas disease later in life [13]. Congenital Chagas disease is associated with premature rupture of the membranes and preterm delivery, and the newborn can show nonspecific symptoms similar to that observed in TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes) syndrome. Rarely, severe morbidities such as meningoencephalitis and cardiomyopathy have been observed [13]. Clinical features of congenital *T cruzi* are more severe for infants of mothers with human immunodeficiency virus (HIV)-*T cruzi* coinfection, including neurological sequel [14–17]. In addition, high parasitic load in umbilical cord is associated with increased severity of congenital Chagas disease in infants [13]. Neonatal mortality was high in early publications but low in recent ones. The possible association with miscarriages and stillbirths is controversial [8]. Uninfected babies of seropositive mothers are healthy.

Prevention and Treatment

Vector control can prevent maternal infection and serve as a primary prevention strategy for congenital *T cruzi*. Data also suggest vector control programs may potentially decrease the risk of MTCT and the severity of congenital Chagas disease by decreasing maternal parasitic load [18]. Congenital transmission rates are lower in nonendemic countries compared with endemic countries [19], and congenital Chagas disease in Bolivia has been less symptomatic in recent periods [20].

In addition to vector control, early diagnosis and treatment of congenital *T cruzi* infection is recommended [21]. Antitrypanosomal treatment is contraindicated during pregnancy [21, 22]. Seropositive mothers are screened during prenatal care or delivery and their offspring are diagnosed and treated. The critical elements for a successful congenital *T cruzi* prevention program include political commitment, health personnel motivation, and population awareness [23].

Treatment options are limited to 2 drugs, benznidazole (BZ) and nifurtimox [21]. These drugs are well tolerated by newborns. The length of the treatment is 30–60 days, which often causes logistic difficulties in the field. Implementation science is being used to identify new ways to improve follow-up of infants of seropositive mothers and treatment compliance. Mobile Health approaches are promising and should be explored further [24]. In some countries, availability of drugs is also an issue [25].

Treatment of children is well tolerated and effective in 50%–70% of the cases, and it could also potentially decrease the risk of future congenital transmission [22]. Sosa-Estani et al [26] observed 16 women treated for Chagas disease during their childhood and found that none of their 32 infants were congenitally infected; however, transmission rates are relatively low [19], and this result would need to be confirmed by large prospective studies.

Murcia et al [27] found no case of congenital transmission among 10 *T cruzi*-seropositive women treated before pregnancy; treatment during preconception may potentially prevent congenital transmission, but it requires further evaluation. Bisio et al [28] report on a case study of an HIV-*T cruzi* coinfected pregnant woman who was treated safely with BZ during pregnancy and congenital transmission of *T cruzi* was prevented; this finding requires further study of the safety and efficacy of treating mothers during pregnancy. In addition, development of treatment that is tolerated during pregnancy would provide an important alternative.

Epidemiology

A recent systematic review concluded that congenital transmission of *T cruzi* occurs in 5.0% of infected women in endemic countries [19]. In nonendemic countries, congenital *T cruzi* infection occurs in approximately 2.7% of infected pregnant women [19]. With growing migration from Latin America, congenital *T cruzi* has been reported with increasing frequency in areas nonendemic to *T cruzi,* including Spain [29, 30] and the United States [31]. Other countries of migration for Latin Americans have documented chronic Chagas in adults [32], perhaps suggesting future areas for monitoring and surveillance of congenital *T cruzi*.

Maternal parasitic load has been associated with congenital transmission [6, 13, 33, 34]. Among pregnant *T cruzi*-infected women in Bolivia, Hermann et al [33]

observed increased risk of congenital *T cruzi* transmission for women with high maternal parasitic load. Rare cases of acute *T cruzi* infection during pregnancy, characterized by higher parasitemia relative to chronic infection, provide further support, where acute infection was associated with increased risk of congenital infection [35]. In addition, maternal age has also been associated with congenital *T cruzi* infection; however, study findings have been inconsistent. Investigators have reported higher odds of *T cruzi* with increasing maternal age [6, 36]. Another study indicates higher risk of congenital *T cruzi* infection was associated with younger maternal age, perhaps a result of recent maternal infection [20]. Congenital *T cruzi* infection has also been observed to cluster in families [37]. Congenital transmission can occur across all pregnancies for an infected mother [38].

Another potentially important determinant of congenital transmission is the strain of the parasite. *T cruzi* parasites are composed of 6 genetic lineages (discrete typing units TcI–TcVI) [39]. All of the *T cruzi* lineages have been observed in congenitally infected infants with the exception of TcIV [40–42]. The role of *T cruzi* lineages on congenital transmission is not well characterized, and it is an important area for further investigation. Geographic difference in congenital *T cruzi* infection may be a result of the distribution of parasitic strains. However, the impact of different diagnostic techniques used across studies and geographic regions may also contribute to differences observed. Determinants of the geographic differences are not well understood.

The immunological state of the mother [6, 33–35] and fetus [16, 43–46] may be important for congenital transmission. Hermann et al [33] observed that decreased maternal immune response to parasitic antigens was associated with increased risk of congenital transmission. In addition, fetal immune response against *T cruzi* parasites may also influence congenital infection. Proinflammation markers against *T cruzi* have been observed in uninfected infants of *T cruzi*-infected mothers, and the production of fetal immune response is limited or absent for congenitally infected infants [43, 44]. The role of maternal and fetal immune health on congenital transmission is not well understood and is an important area of research with potential implications for development of diagnostic tools and treatment.

A few small studies on HIV-*T cruzi* coinfection suggest HIV infection may dramatically increase the rate of congenital transmission [47, 48]. Scapellato et al [47] report 100% congenital transmission of *T cruzi* among HIV-*T cruzi* coinfected mothers ($n = 3$) and 10.9% in mothers only infected with *T cruzi* ($n = 91$). Larger studies are required to examine the role of maternal HIV infection on transmission of congenital *T cruzi*.

Mechanisms of Transmission

T cruzi in maternal blood is most likely transmitted to fetus during the second or third trimester following the opening of the placental intervillous space [16]. The specific routes for congenital transmission of *T cruzi* are unclear, but several general routes of transmission have been examined in the literature. It may cross transplacentally through invasion of trophoblasts [16]. However, histopathology analyses of placenta from congenital *T cruzi* cases have not provided strong evidence of parasite invasion of trophoblasts, where studies have observed parasites in villous trophoblasts and in villous stromal cells [49, 50] and other studies did not observe parasites in trophoblasts [16].

Another path is through other areas of the placenta without trophoblast protection. Among congenital *T cruzi* cases, parasites have been observed in association with inflammation of the umbilical cord and chorionic plate, suggesting parasites may pass through areas of the placenta without trophoblast protection [16]. Breaches and tears that may occur during delivery are also potential routes of congenital transmission of *T cruzi* [16]. Another potential path is through parasites that reach the amniotic fluid; however, there is very little supportive evidence for this mechanism of congenital transmission [40]. Likewise, postnatal transmission of *T cruzi* through lactation also has limited support [16].

Main Research Gaps

Table 1 provides a summary of areas of research that require further scrutiny. There are gaps in the literature that undermine control and elimination of congenital *T cruzi* infection. Establish-ing routine surveillance and monitoring of congenital infection in endemic and nonendemic settings is an important step. Accurate *T cruzi* prevalence estimates, particularly among pregnant women, are a challenge for research and prevention of congenital transmission. Understanding the burden of *T cruzi* infection in pregnant women is critical in building efforts to eliminate congenital infection in endemic and nonendemic regions.

A key tool for surveillance programs is valid and reliable diagnostic tools. Current congenital infection testing strategies require adherence to a lengthy follow-up schedule. Research to develop new diagnostic tools that work early at birth or could be used to test cord blood would help identify infected infants for treatment and prevention. Another avenue that could provide significant benefit is the development of *T cruzi* treatment during preconception and pregnancy, areas that have received little attention. To complement research on diagnostic tools, developing effective treatment options with shorter treatment course and

Table 1. Research Gaps: Important for Eliminating Mother-to-Child Transmission of *Trypanosoma cruzi*

Diagnostics, Prevention, and Treatment
• Evaluate new strategies to improve follow-up and treatment of congenital infection with existing therapies
• Develop new diagnostic tests with high validity and reliability for timely detection of congenital and maternal *T cruzi* infection
• Develop treatment during preconception and pregnancy to reduce congenital transmission
• Develop new drugs with shorter treatment courses and fewer side effects
Epidemiology, Pathophysiology, and Immunology
• Establish routine surveillance and monitoring of congenital *T cruzi* in endemic and nonendemic settings
• Understand maternal, fetal, and parasitic characteristics that may contribute to transmission and clinical symptoms of congenital *T cruzi*
• Characterize mechanisms for congenital transmission during pregnancy, delivery, and lactation
• Estimate the relation between maternal *T cruzi* infection and fetal and neonatal immune health
• Examine the impact of pregnancy on the natural history of *T cruzi* infection and characteristics affecting prognosis
• Estimate burden and role of reinfection and multistrain infection on congenital transmission
• Assess the impact of vector control on maternal parasitic load and congenital transmission

reduced side effects is also important. Operational research is also needed to develop and evaluate new strategies to improve follow-up for existing screening and treatment protocols.

The characteristics important for congenital transmission are not well understood. Epidemiologic studies with longitudinal follow-up are required to examine maternal, parasitic, and fetal characteristics that facilitate transmission and clinical symptoms in infants. These cohort studies will provide a platform to identify mechanisms and characteristics during pregnancy, delivery, and lactation and to examine the role of contextual factors, including vector control on congenital transmission and clinical symptoms. Data from these studies can provide immeasurable benefit for developing diagnostic, prevention, and treatment tools that can work to eliminate congenital transmission.

CONCLUSIONS

T cruzi infection is a neglected tropical disease common in Latin America and increasingly becoming a global public health problem due to population migration. Investment in the development of diagnostic, prevention, and treatment tools have been slow. There is an urgent need to address research gaps, including the development of diagnostic tools, strategies to improve follow-up for existing screening protocols, and expanding treatment options, as well as designing studies to understand characteristics important for transmission and clinical symptoms of congenital *T cruzi* infection.

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