



## REVIEW ARTICLE

# Mother-to-child Chagas disease transmission: The challenge of detection and prevention in areas without the risk of vectorial transmission

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## Abstract

Chagas disease (CD) is caused by the parasite *Trypanosoma cruzi*. Although it is endemic in many Latin American (LA) countries, mother-to-child transmission has caused it to expand to other countries and continents. In places where vector transmission is controlled or absent, the epidemiological importance of *T. cruzi* transmission of the infected mother to her child during pregnancy or childbirth (i.e., perinatal CD) increases. In countries where CD is not endemic, CD screening should be performed in pregnant or fertile women who are native to LA countries or whose mothers are native to LA countries. Diagnosis is established by detecting anti-*T. cruzi* IgG antibodies in a serum or plasma sample. Antiparasitic treatment cannot be offered during pregnancy, and since the majority of infected newborns are asymptomatic at birth, a diagnosis is made by direct observation or concentration (microhematocrit) or by using molecular testing techniques. Once the infected child receives a diagnosis, it is essential to offer treatment (benznidazole/nifurtimox) as soon as possible, with good tolerance and effectiveness in the first year of life. Even if the diagnosis is negative at birth, the newborn must be followed up for at least the first 9 months of life.

## KEYWORDS

congenital Chagas disease, mother-to-child transmission, perinatal transmission, prevention, screening, treatment, *Trypanosoma cruzi*, vertical transmission

## 1 | INTRODUCTION

Chagas disease (CD) is a parasitic disease caused by the flagellated protozoan *Trypanosoma cruzi*, a serious health issue that is endemic in many Latin American (LA) countries. However, due to migratory phenomena, its presence has expanded to other countries and continents.

It is currently estimated that CD affects more than 6 million people worldwide,<sup>1</sup> of which 1.2 million are women of childbearing age.

*T. cruzi* infection has several transmission routes: vectors (triatomine insects), oral (consumption of contaminated food and/or drinks), organ transplantation, blood transfusions, and mother-to-child during pregnancy or at the time of delivery, known as congenital CD (CCD).

Since the early 1990s, the countries afflicted by CD, with the support and leadership of the Pan American Health Organization (PAHO), have taken steps to lessen CD's impact on population health,<sup>2,3</sup> resulting in significant advances such as a substantial

reduction in the number of new cases of domestic vector transmission, prenatal monitoring, and the implementation of universal screening for blood and organ donors, among other initiatives.

Currently, CCD plays a prominent significant epidemiological role. In LA countries, the prevalence of CD in pregnant women is 0.30% to 40%, with a mother-to-child transmission rate of 4% to 10%.<sup>4</sup> CD has a very high socioeconomic and human cost, given that 30% of infected people if not treated will develop heart and/or digestive pathologies such as dilated cardiomyopathy and arrhythmias, megacolon, or megaesophagus that can lead to a range of serious health consequences, including disability and death.<sup>5</sup> The standard treatment for adult nonpregnant patients is 5 to 8 mg/kg of benznidazole per day divided into two doses orally for 60 days. In a recent study of women with CD treated prior to pregnancy, a rate of treatment failure was detected in only 7.9% and the *T. cruzi* mother-to-child transmission rate was 0% among treated women versus 13.2% among untreated women.<sup>6</sup> Thus, treating infected women of childbearing age prevents CCD by reducing the parasitaemia and contributing to the eradication of CD.

Even though in 2006 the World Health Organization (WHO) included CD as one of the neglected tropical diseases (NTDs), there is still a significant debt of care owed to the people who are affected by late diagnoses and limited access to etiological treatment. It is therefore a challenge and an ethical need that calls for immediate action of the different actors of the health teams.

The WHO NTD roadmap suggests that, in order to completely remove the risk of mother-to-child transmission, all CD-infected infants should be treated by 2030 and all women should have access to diagnosis and treatment.<sup>7</sup> To achieve this objective, in 2021 the Ibero-American General Secretariat (IAGS) created the Initiative "No Baby With Chagas: the Way to New Generations Free of Chagas", of which Spain is one of the full members and the Fundación Mundo Sano its technical unit.

This article provides a comprehensive overview of CCD, explores the current state of CD, and offers some practical recommendations to guide gynecologists-obstetricians and other professionals involved in pregnancy control, to contribute to the elimination of mother-to-child transmission of CD. The article combines the review of existing literature with the consensus of experts and opinion leaders on this topic.

## 2 | EPIDEMIOLOGY OF CD

In 2008, 11% of the more than 38 million immigrants living in Europe came from LA countries and more than 4 million were from countries where CD is endemic.<sup>8</sup> In 2009, 53 000 children were born from LA mothers, of whom 1347 to 2521 babies were born from mothers infected with the parasite. In Europe, there is a very low level of diagnosis, estimating that between 94% and 96% of expected cases are not diagnosed.<sup>8</sup> Therefore, the WHO recommends the globalization of efforts to control and eliminate CD.

Migrants infected with *T. cruzi* have been identified in Australia, Canada, France, Germany, Italy, Ireland, New Zealand, Spain, Switzerland, and Japan, among others (Figure 1).<sup>9</sup> In the United States, it is estimated that more than 300 000 individuals are infected by the parasite.<sup>10</sup>

To try to control congenital transmission of the disease, a series of measures have been proposed,<sup>9</sup> which are summarized in Table 1.

## 3 | TRANSMISSION AND INFECTION OF CD

CD is a zoonosis in which humans serve as unintentional hosts. The majority of transmissions occur through the feces of triatomine insects (*Hemiptera: Reduviidae*) that act as vectors, known as vinchucas or kissing bugs<sup>8</sup> (Figure 2). In addition, during pregnancy or childbirth, the infection is also transmitted from the infected mother to her child.<sup>4</sup> Because CD is endemic, many LA countries have implemented strategies to reduce vector transmission, such as the use of insecticides, housing improvement, or CD education, in addition to the universal screening of blood donors; mother-to-child transmission has become the primary source of transmission in areas where CD is not endemic.<sup>7</sup>

Depending on the route of transmission, the incubation period in acute infection varies: transcutaneous transmission is between 1 and 2 weeks, oral transmission between 3 and 22 days, and congenital transmission up to several weeks after birth.<sup>8</sup> CD has two phases, acute and chronic, which can occur with/without evident organic abnormalities and whose characteristics are summarized in Table 2.<sup>11</sup>

Most cases of CD are asymptomatic. In nonimmunocompromised patients, the acute phase usually resolves spontaneously, after which untreated patients enter the chronic phase, which can last a lifetime without obvious organic involvement. However, after 10 to 30 years, up to 30% of patients will develop chronic symptomatic manifestations.<sup>11</sup>

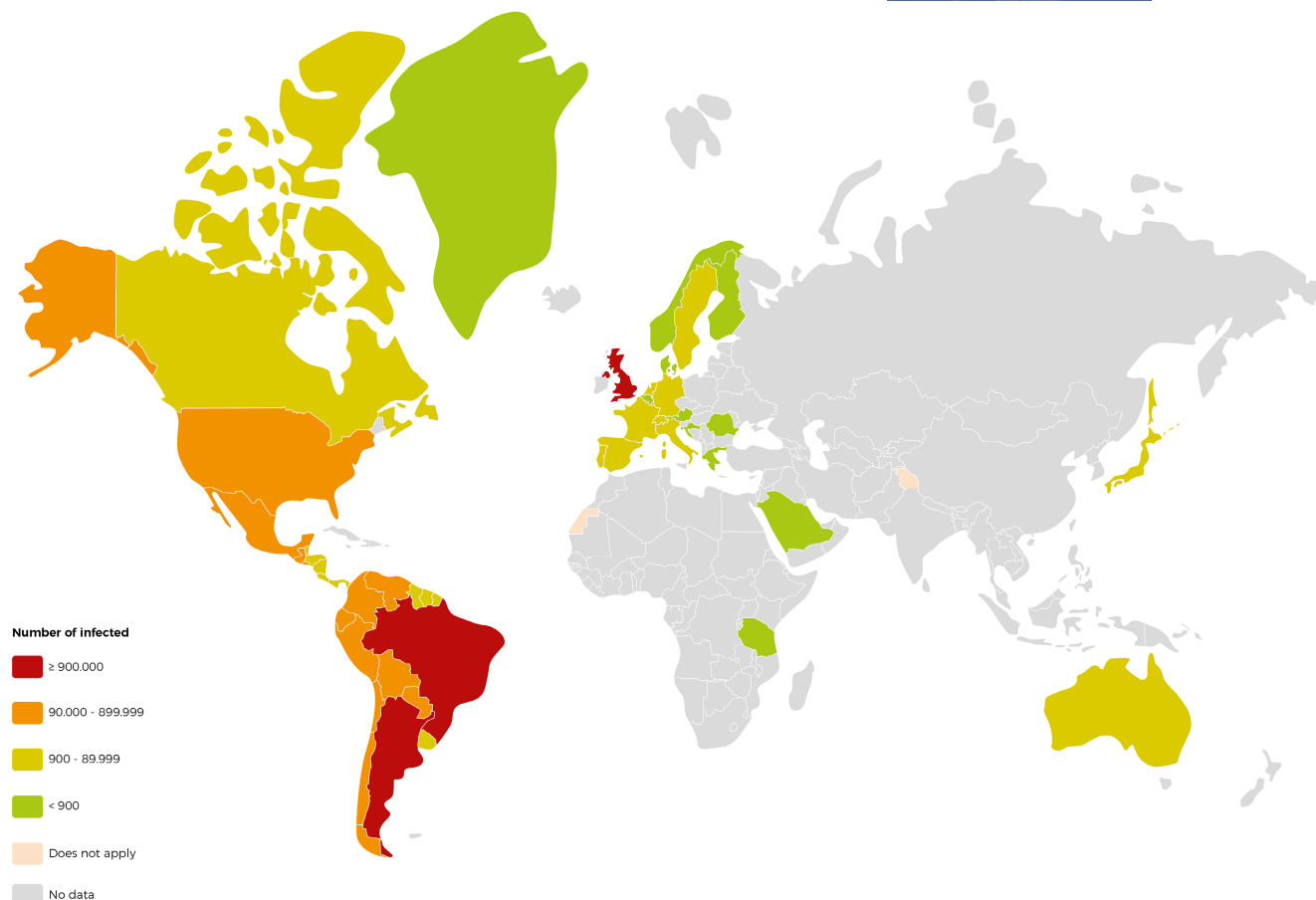
## 4 | MOTHER-TO-CHILD TRANSMISSION OF CCD

Congenital transmission of CD is the main route of transmission in areas without active vector transmission. CCD is defined as the identification of parasites in newborns at birth or by specific antibodies of nonmaternal origin at 10 months of age.<sup>12</sup> The risk of mother-to-child transmission is estimated to be between 5% and 12%, particularly high in countries where CD is endemic.<sup>13</sup>

CCD is an infection that can be asymptomatic, and only 10% of infected children will show clinical manifestations of the disease.

Transmission is possible at any stage of the disease, whether acute or chronic, in each pregnancy, and in successive generations.<sup>14</sup> The factors affecting the spread of CCD are summarized in Table 3.<sup>7</sup>

Maternal parasitemia appears to be the most important factor in the transmission of CCD,<sup>6</sup> and when it rises (i.e., in acute disease



**FIGURE 1** Chagas disease (CD) infection prevalence scheme in countries where CD is and is not endemic.<sup>14</sup> Adapted from Rassi and Marin-Neto.<sup>11</sup>

**TABLE 1** Classification of primary, secondary, and tertiary prevention measures in reducing congenital transmission of CD.

Prevention types	Characteristics
Primary prevention	Systematic serological screening of all fertile-aged women from EA Treatment of cases detected prior to pregnancy
Secondary prevention	Systematic serological screening of all pregnant women from EA Detection of cases for proper management of the newborn and mother after delivery
Tertiary prevention	Detection of infected neonates born to infected mothers before the first year of life, offering treatment and subsequent follow-up Screening of other children and relatives of infected women

Note: Adapted from Soriano-Arandes et al.<sup>9</sup>

Abbreviations: CD, Chagas disease; EA, endemic area.

and/or if chronic infection is reactivated during pregnancy or in immunosuppression), it increases the risk of transmission. CCD is transmitted through the transplacental hematogenous route, causing placentitis with subsequent placental necrosis, resulting in miscarriage, stillbirth, or preterm delivery.<sup>15</sup>

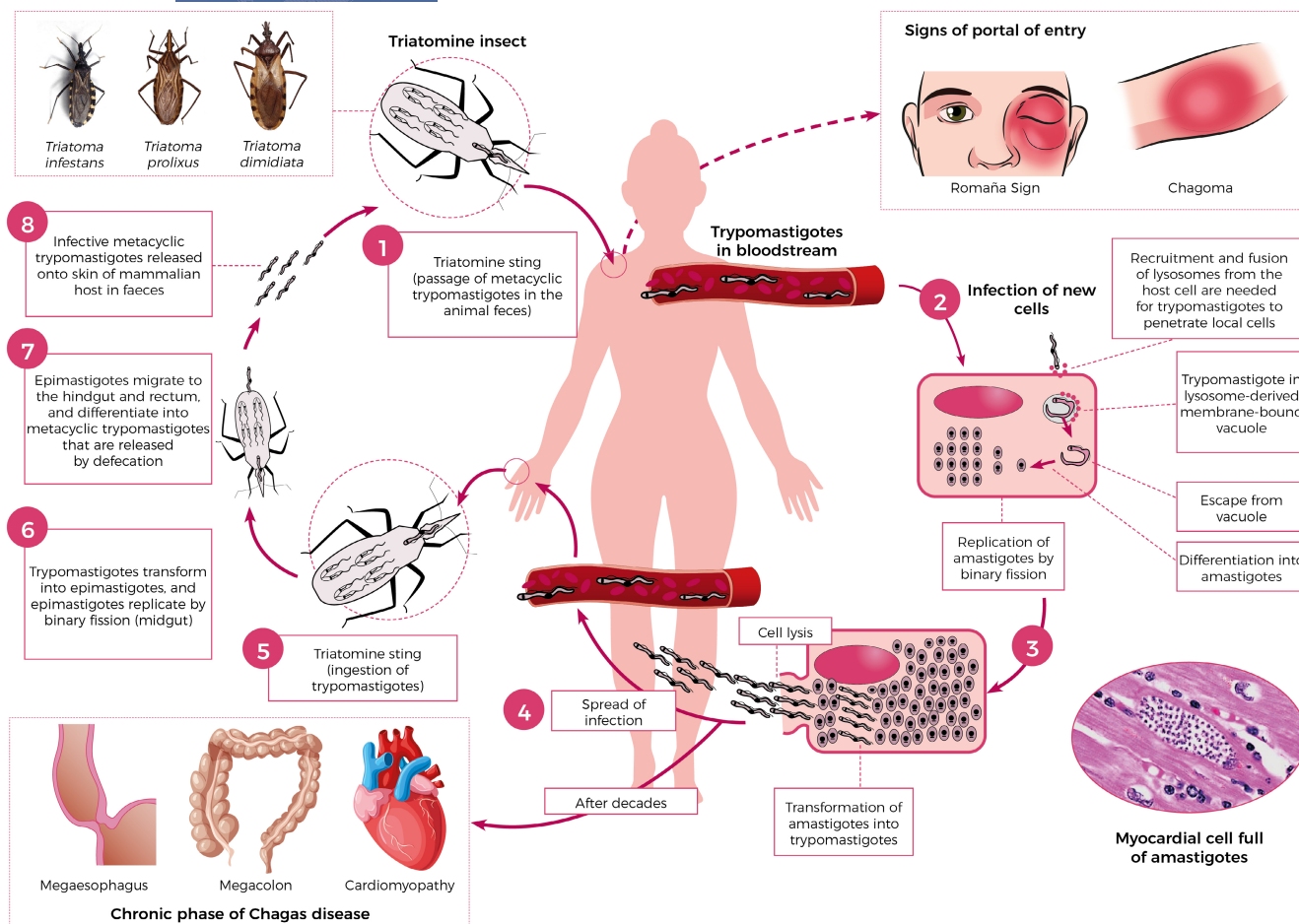
Unfortunately, given the potential teratogenicity of drugs, congenital transmission cannot be prevented by treating the mother during pregnancy.

Breastfeeding should not be interrupted since transmission through breast milk is not clearly established. Interruption may only be considered if there is bleeding or damage of the nipples,

the woman is in the acute phase, or there is a reactivation by immunosuppression. In these cases, milk may be extracted and heat-treated (pasteurization or microwave) prior to administration to the newborn.<sup>16</sup>

## 5 | DETECTION OF CD IN WOMEN AND PREGNANCY MONITORING

Since 2002, the WHO has recommended screening for CD in women and newborns (Table 4) who are at risk in LA countries.<sup>14</sup>



**FIGURE 2** Transmission of Chagas disease occurs through contact with the feces of triatomine insects (Hemiptera: Reduviidae). These blood-sucking insects often defecate while feeding through the host's skin, most commonly in the facial area. The feces contain trypomastigote forms that penetrate through the skin or mucous membranes and into the bloodstream, invade host cells, and differentiate into intermediate epimastigotes or replicative amastigotes. After successive divisions, the amastigotes transform into trypomastigotes that are capable of invading other cells and, in turn, can be taken up by vectors to be eliminated by the feces again and infect another host.<sup>14</sup> Modified from Rassi and Marin-Neto.<sup>11</sup>

**TABLE 2** Description of the stages of CD and its main characteristics.

Phase	Duration	Characteristics
Acute	4–8 weeks	Asymptomatic 10%: fever, inflammation, or edema at the site of inoculation, lymphadenopathies, and hepatosplenomegaly If transcutaneous transmission: nodule at the site of inoculation (Chagoma); if near the ocular mucosal it can cause a painless eyelid edema (Romaña sign) 5%–10%: myocarditis or meningoencephalitis (children)
Chronic	Lifelong	30%: symptomatic 10%–15%: gastrointestinal dysfunctions (megacolon and/or megaesophagus) 20%–30%: heart diseases (cardiomyopathies)

Note: Adapted from Soriano-Arandes et al.,<sup>9</sup> Rassi and Marin-Neto,<sup>11</sup> Suárez et al.<sup>12</sup>  
Abbreviation: CD, Chagas disease.

Although the majority of pregnant women are asymptomatic, related processes such as abortion, neonatal death, fetal growth abnormalities (low weight for gestational age or intrauterine growth restriction), hepatosplenomegaly, anemia, or visceral dilations, have been described during pregnancy.<sup>11</sup>

*T. cruzi* does not infect the fetus before 12 weeks, so it will not be associated with fetal malformations. Nevertheless, the

obstetrician must perform an adequate control of fetal morphology and growth, rule out premature birth and premature rupture of membranes, and monitor other signs of fetal vitality.<sup>14,17</sup> In addition, due to the risk of CD infection in an immunocompromised receptor, it is crucial to advise against cord blood donation, bone marrow transplant, or blood donations from CD-positive pregnant women.<sup>14</sup>

TABLE 3 Factors affecting the transmission of CD.

Factors	Characteristics
Maternal	Maternal parasitemia: the most important. The higher the parasitemia, the higher the risk of contagion Genetic regulation of the immune response of the fetus/newborn and the mother Mother's age: if young, it could be assumed a more recent infection Malnutrition, poverty, and poor socio-sanitary conditions
Gestation	Period of pregnancy in which the infection occurs: most severe in the 1st trimester Previous transmissions in other pregnancies and trypanocide treatment was not administrated Cesarean delivery avoiding intestinal colonization (not accepted by all authors) Twin pregnancy seems to decrease T cell-mediated immunity
Parasite	Mother's geographical origin that determines the subtypes of infective parasite Virulence of the infective strain Coinfection with HIV (likely due to maternal immunosuppression)

Note: Adapted from Shikanai Yasuda<sup>7</sup> and Edwards et al.<sup>4</sup>

Abbreviation: CD, Chagas disease.

TABLE 4 Target population that should undergo CD screening.

Native women from EA
Women whose mother is native from EA
Women who have traveled to an EA and engaged in activities that carry risk of contracting CD (long-term stay or visit to rural areas, spending the night outdoors or in camping tents or rural houses made of plant materials such as straw or wood, drinking unpasteurized fruit juices or sugarcane juice)
Women who have received blood transfusions in an EA

Note: Adapted from Carlier et al.<sup>14</sup>

Abbreviations: CD, chagas disease; EA, endemic area.

## 6 | CONSEQUENCES OF CCD IN NEWBORNS AND CHILDREN

Although nearly 80% (40%–100%) of newborns will remain asymptomatic, it is necessary to rule out the presence of signs and symptoms of systemic involvement, which are typical of the acute phase of the disease. Clinical manifestations, such as non-specific symptoms that may be difficult to distinguish from other infections, including fever, splenomegaly, edema, anasarca, skin lesions, purpura, jaundice, anemia, or thrombocytopenia, may not develop until weeks after delivery.<sup>12</sup> Other characteristic manifestations including meningoencephalitis, neurological alterations, or myocarditis, may appear less frequently but with higher mortality risk.<sup>18</sup>

In countries where CD is not endemic, mortality is very low or anecdotally associated with previously undiagnosed cases.<sup>12</sup> As a result, even if physical examination is normal, it is recommended that all newborns with CD undergo additional tests, including blood cell count, blood and urine biochemistry, chest x-ray, brain and abdominal ultrasonography, funduscopy, echocardiography, and electrocardiography.<sup>5,14</sup> If not treated, the condition could progress to a chronic phase and 30% of patients may develop organic abnormalities, increasing their risk of premature death and severe disability.<sup>12</sup> This is why it is essential to start treatment as soon as the CCD has been diagnosed, given the high rate of cure demonstrated by parasitological and immunological studies that

reaches 90% to 100% of cases if treatment started in the first year of life,<sup>19</sup> with few side effects.<sup>14</sup> If the diagnosis was not made at birth, it is essential to monitor the newborn of a mother with CD for at least the first 9 months. After the first year of life, the study should be conducted in children from areas where CD is endemic or in children of mothers with CD who were not monitored during the neonatal period.<sup>4,11</sup>

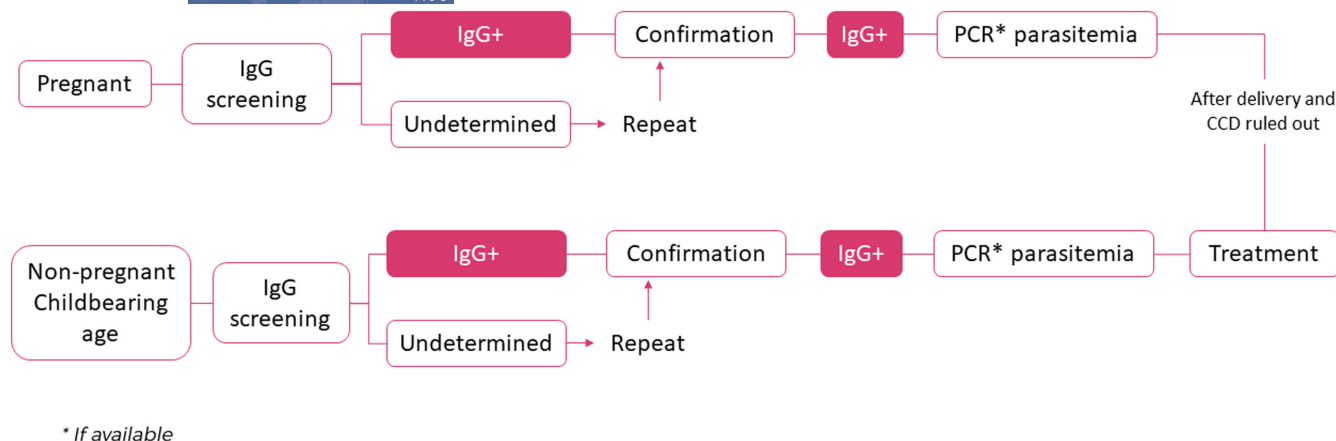
## 7 | SCREENING AND DETECTION OF CCD

To detect *T. cruzi* infection in pregnant or fertile women, it is important to implement a screening strategy. Because most affected women are in the chronic phase of infection, their diagnosis is established by high-sensitivity tests, detecting IgG anti-*T. cruzi* antibodies in a serum or plasma sample using chemiluminescence immunoassay or enzyme-linked immunosorbent assays.<sup>11,15</sup> While a negative test result rules out infection, a positive finding must be confirmed by a second test of greater diagnostic specificity, such as indirect immunofluorescence, immunochromatography, Western blot, or a different enzyme-linked immunosorbent assay from the one used in screening.<sup>11,15</sup>

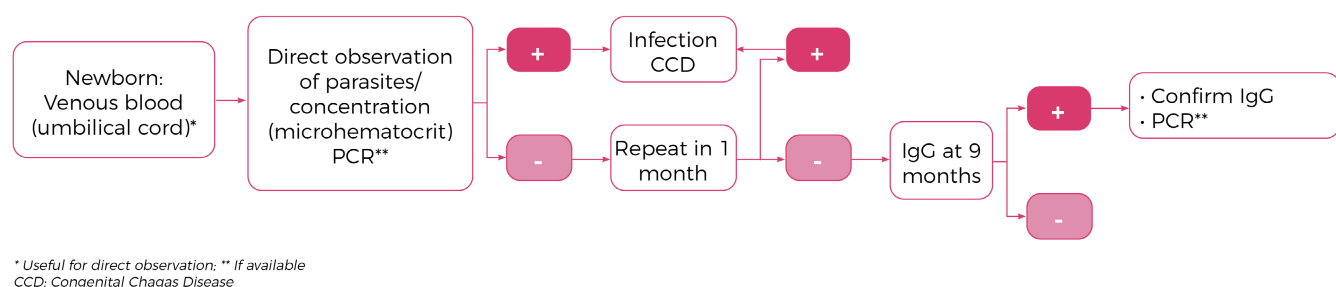
In pregnant women, in whom it is not possible to establish a diagnosis in the first trimester, it is recommended to perform immunodiagnostic studies in future controls with a detailed anamnesis of risk factors. In women with a positive diagnosis, it is advisable to study parasitaemia by polymerase chain reaction (PCR) if available.<sup>6,20</sup> (Figure 3).

Once a pregnant woman is diagnosed with having CD, screening should be performed in other siblings and her mother.<sup>12,15</sup>

To determine the presence of infection in the newborn of a mother with CD, it is recommended to take a sample of peripheral venous blood in a tube with ethylenediaminetetraacetic acid. In cases where this is not feasible, cord blood may be used if there is no contamination with maternal blood, via direct observation or concentration (microhematocrit), checking for parasites in motion within 8 hours of sampling. If available, the remaining sample should be analyzed by PCR or other molecular method.<sup>20–22</sup>



**FIGURE 3** Screening scheme for Chagas disease in pregnant women. CCD, congenital Chagas disease; PCR, polymerase chain reaction. Diagram created by author.



**FIGURE 4** Screening scheme for congenital Chagas disease (CCD) in newborns. PCR, polymerase chain reaction. Diagram created by author.

A positive result at birth confirms the infection. However, if negative, both determinations must be repeated 1 month later. If it remains negative, serological screening (IgG) can be performed at 9 months of age<sup>15,23</sup> (Figure 4). If it is also negative, the infection can be ruled out, while if it is positive, it must be confirmed with a second serological test and, if available, a PCR test in order to determine the parasitaemia, which, in posttreatment follow-up, acts as a marker of therapeutic failure.<sup>24</sup>

The study of serology of the newborn before 8 months of age is not recommended to avoid detection of maternal antibodies.<sup>8,15</sup>

## 8 | MANAGEMENT AND FOLLOW-UP OF THE NEWBORN AFTER DIAGNOSIS OF CCD

Once the infected newborn has been diagnosed, it is essential to administer trypanocide treatment as soon as possible, as it has shown good tolerance and optimal effectiveness when administered during the first year of life. If treatment is delayed, there may be more adverse effects and the disease may progress to chronicity.<sup>22</sup> In addition, because the antibody titer against *T. cruzi* can remain positive for years, it could be difficult to evaluate the efficacy of the treatment and prognosis of the disease.<sup>6</sup> Treatment with benznidazole and nifurtimox in children has been approved by the FDA. According to CD treatment guidelines, all cases of acute illness, reactivation

**TABLE 5** Target population that should be treated for CD.

Recommendation for starting CD treatment
Newborns and children with CCD
Other infected children after disease is detected in the mother
Girls and nonpregnant women of fertile age with CD
Adults with acute CD
Adults with asymptomatic CD without clinical manifestations (indeterminate CD) with a high risk of reactivation due to the need for immunosuppressive therapy (e.g. HIV and organ transplant)

Note: Adapted from Pérez-Molina and Molina.<sup>25</sup>

Abbreviations: CCD, congenital Chagas disease; CD, Chagas disease.

of infection, and individuals younger than 18 years, should be treated<sup>12,25</sup> (Table 5).

Benznidazole is used frequently for its better tolerability and efficacy than nifurtimox. Although side effects have also been reported (Table 6),<sup>8</sup> it is better tolerated in children than in adults.<sup>15,25</sup> Benznidazole is not contraindicated in mothers with CD during breastfeeding, because of the low transmission of the drug in breast milk and the low potential of exposure to the newborn.<sup>16</sup>

In the acute phase, treatment is effective in 80% of cases, reaching 100% if it is administered during the first year of life. In the chronic phase, there is no universal consensus about when to start



TABLE 6 Schedule of doses and most frequent side effects of the treatments available for CD.

Drug	Dose	Side effects
Benznidazole	5–8 mg/kg per day divided into 2 oral doses for 60 days, never less than 30 days	Hypersensitivity reactions Rash Fever
Nifurtimox	10–20 mg/kg per day divided into 3 doses for 60 days if children <40 kg 8–10 mg/kg per day divided into 3 oral doses if children >40 kg	Nausea and vomiting Neurological disorders (possible discontinuation of treatment)

Note: Adapted from Abras et al.<sup>8</sup>

Abbreviation: CD, Chagas disease.



FIGURE 5 Evolution from birth to 3, 8, and 9 months of age of a girl with congenital Chagas disease. Hepatosplenomegaly decreases after early treatment. Currently, the girl is in good health and both serology and polymerase chain reaction results are consistently negative.

treatment, but evidence suggests that it could have a potential benefit especially in young adults and in women of childbearing age.<sup>6,15</sup>

After treatment is administered, it is important to perform close monitoring to ensure good adherence to treatment, detect possible adverse events, and assess parasitic clearance by PCR, which will be key to early detection of therapeutic failure.<sup>6</sup> When serology is positive, monitoring should be extended to confirm the complete clinical and microbiological cure of children,<sup>14</sup> which can occur at around 9 to 12 months if treated from birth but can last for years if treatment is delayed (Figure 5).

## 9 | CONCLUSIONS

The following conclusions can be drawn from the current review. Migratory movements have transformed CD into a global public health issue. In areas and countries without risk of vector transmission, the main concern is controlling the risk of CCD. It is advisable to follow a protocol that includes screening and diagnosis of both pregnant women and newborns to avoid mother-to-child transmission. It is important to educate health care providers about CD and encourage them to counsel pregnant women and women of childbearing age for serological screening of *T. cruzi* infection, if possible, before becoming pregnant, and to administer treatment before pregnancy to prevent mother-to-child transmission. If a case of CCD is detected, the mother should be treated after delivery when mother-to-child transmission is ruled out. During pregnancy, trypanocide

treatment is not recommended since it is not known whether the drugs have teratogenic effects on the fetus. The newborn will also need to start treatment as soon as the infection is confirmed. If CCD is not confirmed at birth, close clinical, parasitological, and serological monitoring should be performed to ensure early diagnosis and treatment. Finally, children with CCD younger than 1 year treated with benznidazole have a cure rate greater than 90%. Benznidazole is very effective in preventing long-term CD complications and has few side effects. Postponing treatment has been associated with a progression of the disease to indeterminate chronic stages and a lower rate of subsequent cure.

## AUTHORS CONTRIBUTIONS

Gold S: Drafting/writing. Palacios Gil-Antuñano S: Planning and logistics, Drafting/writing. Abril M: Drafting/writing. Segovia-Hernández M: Drafting/writing. Canelo-Hidalgo MJ: Drafting/writing. Flores-Chávez M: Drafting/writing, Revising, editing, and proofreading. Pelayo-Delgado I: Drafting/writing, Revising, editing, and proofreading.

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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