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Risk factors for vertical transmission of Chagas disease: A systematic review and meta-analysis

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Abstract

Background: Vertical transmission of *Trypanosoma cruzi* infection from mother to infant accounts for a growing proportion of new Chagas disease cases. However, no systematic reviews of risk factors for *T. cruzi* vertical transmission have been performed.

Methods: We performed a systematic review of the literature in PubMed, LILACS, and Embase databases, following PRISMA guidelines. Studies were not excluded based on language, country of origin, or publication date.

Results: Our literature review yielded 27 relevant studies examining a wide variety of risk factors, including maternal age, parasitic load, immunologic factors and vector exposure. Several studies suggested that mothers with higher parasitic loads may have a greater risk of vertical transmission. A meta-analysis of 2 studies found a significantly higher parasitic load among transmitting than non-transmitting mothers with *T. cruzi* infection. A second meta-analysis of 10 studies demonstrated that maternal age was not significantly associated with vertical transmission risk.

Conclusions: The literature suggests that high maternal parasitic load may be a risk factor for congenital Chagas disease among infants of *T. cruzi* seropositive mothers. Given the considerable heterogeneity and risk of bias among current literature, additional studies are warranted to assess potential risk factors for vertical transmission of *T. cruzi* infection.

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Conflicts of interest

The authors report no conflicts of interest.

Ethical approval

None required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2021.02.074.

Keywords

Chagas disease; Vertical infection transmission; Neonatal diseases; Systematic review; Meta-analysis

Introduction

Over 5 million people in Latin America are infected with *Trypanosoma cruzi*, the parasitic agent of Chagas disease (Chagas disease in Latin America: an epidemiological update based on 2010 estimates, 2015). Although transmission most commonly occurs through the triatomine vector ("kissing bug"), vertical transmission from mother to infant accounts for over 20% of new cases (Howard et al., 2014). Like other individuals with Chagas disease, congenitally infected infants have up to a 30% lifetime risk of developing severe and potentially fatal sequelae such as cardiomyopathy, arrhythmias, and gastrointestinal or neurological complications (Bern et al., 2011; Py, 2011).

Antiparasitic therapy is available for *T. cruzi* infection, and congenital Chagas disease is nearly always curable in the first year of life (Picado et al., 2018). Likelihood of cure and tolerability of therapy wane with age. However, the majority of infants with congenital Chagas disease do not receive timely diagnosis and treatment. Infant diagnosis is complex, costly, and may take up to a year, as serology cannot be reliably performed until maternal antibody disappears 8 months after birth (Carlier et al., 2011). Given the limited resources in many endemic settings, better risk stratification is needed to identify maternal, environmental, and sociodemographic characteristics associated with higher vertical transmission rates.

In this systematic review, we aim to identify factors associated with the risk of vertical transmission of *T. cruzi* infection. Specifically, we compared characteristics of cases in which vertical transmission did occur from chronically infected mothers to cases in which it did not. Our review followed Preferred Reporting Items for Systematic review and Meta-analyses (PRISMA) guidelines and was not limited by publication date, country of origin, or language (Moher et al., 2009).

Methods

Search strategy

Searches were performed for relevant literature in PubMed, LILACS, and Embase electronic databases (Figure 1, Table 1). A search was also performed in clinicaltrials.gov to identify ongoing or unpublished studies. The last search was performed on June 20, 2020. There was not a registered protocol.

Study selection

Studies from the searches mentioned above were compiled for further review in Covidence, which removed duplicate studies (Covidence – Better systematic review management, n.d.). Two reviewers screened studies by title and abstract using eligibility criteria determined a

priori (Table 2), and removed irrelevant studies; conflicts were resolved through discussion. Studies of mothers with confirmed serology for *T. cruzi* infection and their infants were included. Acceptable exposures included a broad array of potential risk factors for *T. cruzi* transmission, including maternal, infant, and parasite characteristics. Previous maternal treatment for Chagas disease or known infant sequelae of congenital Chagas disease were not considered in analyses. We included studies that compared these exposures among seropositive women who did or did not transmit *T. cruzi* infection or among infants of seropositive women who did or did not develop congenital Chagas disease. We included infants diagnosed with congenital Chagas disease within 1 year of delivery, as a serological diagnosis cannot be performed until after 8 months of age when maternal antibody has disappeared (Carlier et al., 2011). Infant *T. cruzi* infections diagnosed after 1 year were excluded as these could represent new acute infections. We included empirical interventional or observational study designs, including randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies. Review articles, abstracts, case studies, studies with a single case of congenital Chagas disease, letters and comments were excluded. No studies were excluded based on language, date of publication, publication status, country of origin, or clinical setting. Following title and abstract review, full text articles were screened for inclusion by 2 reviewers using the same eligibility criteria; conflicts were resolved through discussion.

Study assessment

The risk of bias in individual studies was assessed using the Newcastle-Ottawa Scale (NOS), an accepted quality rating tool for observational studies (Supplementary Table 1) (Wells et al., n.d.). This scale evaluates study quality using 8 categories reflecting the selection, comparability, and outcomes of each study. Studies were evaluated by 2 reviewers; conflicts were resolved through discussion.

Data extraction

Data extracted for each study included setting, population, study design, Chagas disease prevalence and congenital transmission rate, and risk factors examined (Table 3). Study data were extracted manually by 2 reviewers; conflicts were resolved through discussion.

Statistical analysis

Data analysis was performed in Stata (version 16). Random-effects meta-analysis was performed for variables examined by multiple studies with sufficiently similar study designs. When the necessary data were not available in the published articles, the original study authors were contacted. If means and standard deviations were not available after contacting the original study authors, these were calculated from the medians and interquartile ranges using established methodology (Wan et al., 2014).

Results

Search strategy

The search identified a total of 1335 publications (Figure 1). The publications underwent screening by title and abstract, and 1274 were determined to be irrelevant. The remaining 61

were screened with full text review. Studies were excluded for ineligible study design (such as no comparison group), ineligible publication type (such as reviews or abstracts), ineligible outcome (such as outcomes besides confirmed congenital infection with *T. cruzi*), full text unavailable, ineligible comparator (such as nonchagasic mothers), or duplicates. Two articles were considered unavailable as the full texts were not available online through any known database, and the original authors did not reply to a request for the article.

Study characteristics and findings

The final analysis included 27 publications, of which 3 were available solely in Spanish (Tables 3 and 4). Studies took place most frequently in Argentina and Bolivia, with 13 studies drawing participants from each country (Alonso-Vega et al., 2005; Bern et al., 2009; Brutus et al., 2010; Bua et al., 2012; Buekens et al., 2018; Burgos et al., 2007; Cardoni et al., 2004; Chaparro and Genero, 2018; Danesi et al., 2020; García et al., 2008; Hermann et al., 2004; Herrera et al., 2019; Juiz et al., 2016; Kaplinski et al., 2015; Martin Suasnabar et al., 2018; Messenger et al., 2017; Negrette et al., 2005; Rendell et al., 2015; Salas et al., 2007; Scapellato et al., 2009; Torrico et al., 2006, 2004; Volta et al., 2016). Other study locations included Honduras, Mexico, Paraguay, and Spain (Basile et al., 2019; Bua et al., 2012; Buekens et al., 2018; Herrera et al., 2019; Juiz et al., 2016; Murcia et al., 2017, 2013). The publications examined a wide variety of potential risk factors for vertical transmission, such as maternal age, parasitic load, parasite and infant genetics, twin births, immunologic factors, and vector exposure. Most studies required at least 2 positive serological tests for maternal diagnosis, per the World Health Organization guidelines (Guidelines for the Diagnosis and Treatment of Chagas Disease, 2019). Infant testing varied more widely between studies. Of the 27 studies, 21 (77.8%) used micromethod testing. Many studies also used a combination of serology (18 studies), polymerase chain reaction (PCR; 11 studies), hemoculture (6 studies), and/or xenodiagnosis (2 studies).

Maternal parasitic load

Several studies examined maternal parasitic load as a risk factor for vertical transmission of *T. cruzi* infection. Two studies were found to have sufficiently similar study designs and laboratory techniques to perform a meta-analysis (Bern et al., 2009; Kaplinski et al., 2015). This analysis indicated that among *T. cruzi* seropositive women, those who vertically transmitted the infection had significantly higher parasitic loads than those who did not (Figure 2). Heterogeneity in this analysis was very low ($I^2 < 0.01\%$). A significant association between higher maternal parasitic load and risk of vertical transmission was found in 5 studies in our review, 4 of which had non-overlapping participants (Table 5) (Bern et al., 2009; Brutus et al., 2010; Bua et al., 2012; Kaplinski et al., 2015; Rendell et al., 2015). Only 1 study found a non-significant trend for higher maternal parasitic load within 1 subpopulation and no significant difference in another subpopulation (Buekens et al., 2018). Several studies found an increased risk of vertical transmission among mothers with positive *T. cruzi* parasitemia, PCR, hemoculture, or xenodiagnosis during pregnancy, which may also be suggestive of higher parasitic load (Alonso-Vega et al., 2005; Bern et al., 2009; Hermann et al., 2004; Murcia et al., 2013; Salas et al., 2007; Scapellato et al., 2009).

Maternal vector exposure

Several studies examined the association between maternal vector exposure and risk of vertical transmission. Five studies found that self-reported past exposure to triatomine bugs in the home or community was significantly associated with lower risk of vertical transmission (Danesi et al., 2020; Kaplinski et al., 2015; Martin Suasnabar et al., 2018; Negrette et al., 2005; Rendell et al., 2015). Two of these studies and 1 other study found that self-reported current exposure to triatomine bugs in the home was not significantly associated with vertical transmission risk (Chaparro and Genero, 2018; Kaplinski et al., 2015; Rendell et al., 2015).

Maternal age

Among 11 non-overlapping studies that reported risk by maternal age, 9 studies found that maternal age was not significantly associated with risk of vertical transmission (Basile et al., 2019; Bern et al., 2009; Bua et al., 2012; Cardoni et al., 2004; Danesi et al., 2020; García et al., 2008; Martin Suasnabar et al., 2018; Negrette et al., 2005; Rendell et al., 2015; Salas et al., 2007). The remaining 2 studies found an increased risk of vertical transmission among younger women (Kaplinski et al., 2015; Torrico et al., 2004). Original study data were available for 10 of the 11 studies through published data or communication with study authors. Our meta-analysis of these 10 studies suggested that maternal age is not significantly associated with risk of vertical transmission among *T. cruzi* seropositive mothers (Figure 3A) and demonstrated an overall effect size (Hedge's g) of −0.52 (95% CI: −1.34–0.31). However, heterogeneity in this analysis was very high (I^2 = 98%), and the forest and funnel plots revealed the study by Torrico and colleagues to be an outlier (Figures 3 and 4). Therefore, we conducted a sensitivity analysis by removing this study, which resulted in much lower heterogeneity (I^2 =54%) with no evidence of bias based on the funnel plot (Figure 3B and 4B), while still suggesting that maternal age was not significantly associated with the risk of vertical transmission (Hedge's g = −0.10 [95% CI: −0.30–0.10]). Although the reasons for Torrico and colleagues' disparate results are unclear, this study included the oldest cohort of women in the review and could reflect changes in which mothers are most likely to participate and return for follow-up in observational studies (Torrico et al., 2004).

Parasite genetics

Three studies considered whether parasite genetics, including discrete typing unit (DTU) and haplotype, were related to risk of vertical transmission (Buekens et al., 2018; Burgos et al., 2007; Herrera et al., 2019). None of these studies identified a clear association between *T. cruzi* DTU and vertical transmission risk, but 1 study found that haplotypes significantly differed between transmitting and non-transmitting cases (Herrera et al., 2019). Specifically, this study found that the non-TcI-H1 haplotype was more common among transmitting than non-transmitting cases.

Other risk factors

Five studies examined various maternal and infant immunologic factors; however, considerable heterogeneity between the studies prevented further analysis (Alonso-Vega et

al., 2005; Cardoni et al., 2004; García et al., 2008; Hermann et al., 2004; Volta et al., 2016). Three studies found that maternal interleukin(IL)-10 was not significantly associated with transmission risk (Cardoni et al., 2004; García et al., 2008; Hermann et al., 2004), while 1 study found an increased risk among women with lower IL-10 (Alonso-Vega et al., 2005). Two studies found an increased transmission risk among women with lower tumor necrosis factor(TNF)-α (Cardoni et al., 2004; García et al., 2008), and 1 study found no significant difference in transmission risk by maternal TNF-R2 level (García et al., 2008). Finally, 1 study found an increased transmission risk among women with higher interferon(IFN)-γ in cord blood (Torrico et al., 2005), while another found an increased risk among women with higher IFN-γ in whole blood incubated with *T. cruzi* lysate (Hermann et al., 2004).

Other potential risk factors examined by multiple studies included twin births, socioeconomic factors, and immunologic factors. In 3 studies assessing risk of vertical transmission among twin births, 2 found an increased risk of vertical transmission (Kaplinski et al., 2015; Rendell et al., 2015), and 1 found no significant difference (Salas et al., 2007). Three studies found no difference in risk among mothers who lived in urban or rural areas (Chaparro and Genero, 2018; Kaplinski et al., 2015; Martin Suasnabar et al., 2018). Finally, several individual studies considered additional risk factors, such as infant genetics, maternal HIV status, infant sex, and maternal clinical form of Chagas disease (Basile et al., 2019; Herrera et al., 2019; Juiz et al., 2016; Messenger et al., 2017; Scapellato et al., 2009).

Risk of bias

The risk of bias in the included publications ranged from moderate to high, assessed by the Newcastle-Ottawa Scale (Supplementary Table 1). The most common limitation was inadequate follow-up or response rates, as most infants did not complete the 9-month follow-up required for serological diagnosis. Another common source of potential bias was lack of controlled analysis, as the majority of included publications did not control for confounding factors such as age, medical history, or socioeconomic status.

Discussion

This study is the first systematic review to examine and assess risk factors for vertical transmission of Chagas disease. We identified 27 relevant publications with significant heterogeneity in study design, population, infant diagnostic methods, and potential risk factors.

A growing body of evidence supports an increased risk of vertical transmission among mothers with a higher parasitic load. Our meta-analysis further supports this association, although it was limited to 2 studies due to differences in study design and laboratory techniques (Bern and Montgomery, 2009; Kaplinski et al., 2015). However, 3 studies not included in the meta-analysis also found a significantly increased risk of vertical transmission among women with higher parasitic loads, while only 1 study found a non-significant trend in the same direction (Brutus et al., 2010; Bua et al., 2012; Rendell et al., 2015). Notably, several studies also found higher transmission rates among women with lower self-reported vector exposure (Danesi et al., 2020; Kaplinski et al., 2015; Martin

Suasnabar et al., 2018; Negrette et al., 2005; Rendell et al., 2015). Although seemingly counterintuitive, this relationship may also be explained by differences in parasitic load. Previous studies have found that women who live in infested homes for extended periods actually have lower parasitic loads, leading to the hypothesis that prolonged vector exposure or superinfection may lead to an enhanced immune response (Rendell et al., 2015). Overall, these results warrant further study of maternal parasitic load as a potential risk factor for transmission to infants. As trypanocidal therapy is contraindicated in pregnant women, these findings suggest that reducing the parasitic load in women of childbearing age before pregnancy could reduce vertical transmission rates (Bustos et al., 2019). Although this review did not specifically examine prior maternal treatment as a risk factor for vertical transmission, multiple studies have demonstrated that trypanocidal treatment of infected women reduces the risk of congenital transmission and should be considered a key target for public health interventions (Fabbro et al., 2014; Moscatelli et al., 2015).

Older age is a known risk factor for maternal *T. cruzi* seropositivity in many endemic countries (Cucunubá et al., 2012), in part due to lifelong vector exposure in endemic areas. Reduced prevalence of infection in younger women is also thought to reflect improvements in safe housing and vector control efforts in recent years (Samuels et al., 2013). However, our meta-analysis suggests that maternal age is not a significant risk factor for vertical transmission. Immunological control of the infection may be relatively stable across age groups, consistent with studies demonstrating no difference in *T. cruzi* parasitic loads by age among young and middle-aged adults (D'Ávila et al., 2018; Rodrigues-dos-Santos et al., 2018).

Some studies in our review suggested that immunologic factors or twin births may play a role in risk of vertical transmission. Overall, maternal inflammatory profile was not clearly associated with risk of vertical transmission, and this topic deserves more focused attention. Twin pregnancies could be more susceptible to congenital infection than singleton pregnancies due to placental insufficiency facilitating transplacental transfer of the parasite or enhanced immune suppression allowing higher maternal parasitic loads. More research is needed to clarify whether twin pregnancies have an increased risk of vertical transmission and, if so, to study the pathogenesis of this risk.

The association between *T. cruzi* genetics and vertical transmission risk is an emerging area of study. *T. cruzi* DTU distribution is known to vary by country, and it has been suggested that this could contribute to variation in vertical transmission rates (Luquetti et al., 2015). One study in our review identified a higher risk of transmission with the non-TcI-H1 haplotype; however, no studies found a difference in DTUs between transmitting and non-transmitting cases (Herrera et al., 2019). Future studies should directly compare both *T. cruzi* DTUs and haplotypes between transmitting and non-transmitting mothers to clarify the role of parasite genetics in vertical transmission.

Our review demonstrates that congenital Chagas disease testing strategies vary widely between studies and countries. The most common diagnostic test remains micromethod, which is subjective and detects less than half of congenital infections (Bern et al., 2009; Messenger et al., 2017). Newer diagnostic methods such as quantitative PCR

and IgM-TESA-blot (Trypomastigote Excreted-Secreted Antigens) are more expensive but outperform older techniques, with significantly higher sensitivity and specificity for detection of *T. cruzi* infection (Castro-Sesquén et al., 2020; Picado et al., 2018). Future studies would benefit from consistently using more sensitive techniques to detect congenital infections.

This systematic review has several limitations, including the scope and quality of the existing literature. Common limitations in the studies included lack of comparability between study groups, lack of control for potential confounding factors, and high loss to follow-up. Poor follow-up is a frequent challenge for congenital Chagas disease studies as infant diagnosis can take 8–12 months for serological results (Alonso-Vega et al., 2005; Bern et al., 2009; Messenger et al., 2017). Many families do not return for long-term follow-up due to financial and travel barriers and low perceived benefit. Many studies relied, at least in part, on micromethod for infant diagnosis of congenital Chagas disease. Given the low sensitivity of micromethod, many infants likely remained undiagnosed. Publication bias could also potentially limit the number of available studies with non-significant results. Finally, it can be difficult to distinguish risk factors for vertical transmission from sequelae of congenital Chagas disease. For example, it is unclear whether infant immunologic factors represent risk factors or sequelae of disease.

Despite the high morbidity and mortality associated with congenital Chagas disease, relatively few studies have examined risk factors for vertical transmission of *T. cruzi* infection. Our current understanding of these risk factors is limited by poor to moderate-quality evidence, a lack of large prospective studies, and significant heterogeneity between studies. However, the existing literature suggests that high maternal parasitic load may be associated with elevated risk of vertical transmission of *T. cruzi*, while maternal age does not appear contributory. Additional high-quality research is needed to further elucidate maternal, environmental, infant, and parasitic risk factors for vertical transmission and to identify high-risk populations. As the literature continues to grow, another systematic review is warranted in 10 years to reassess risk factors for vertical transmission of *T. cruzi* infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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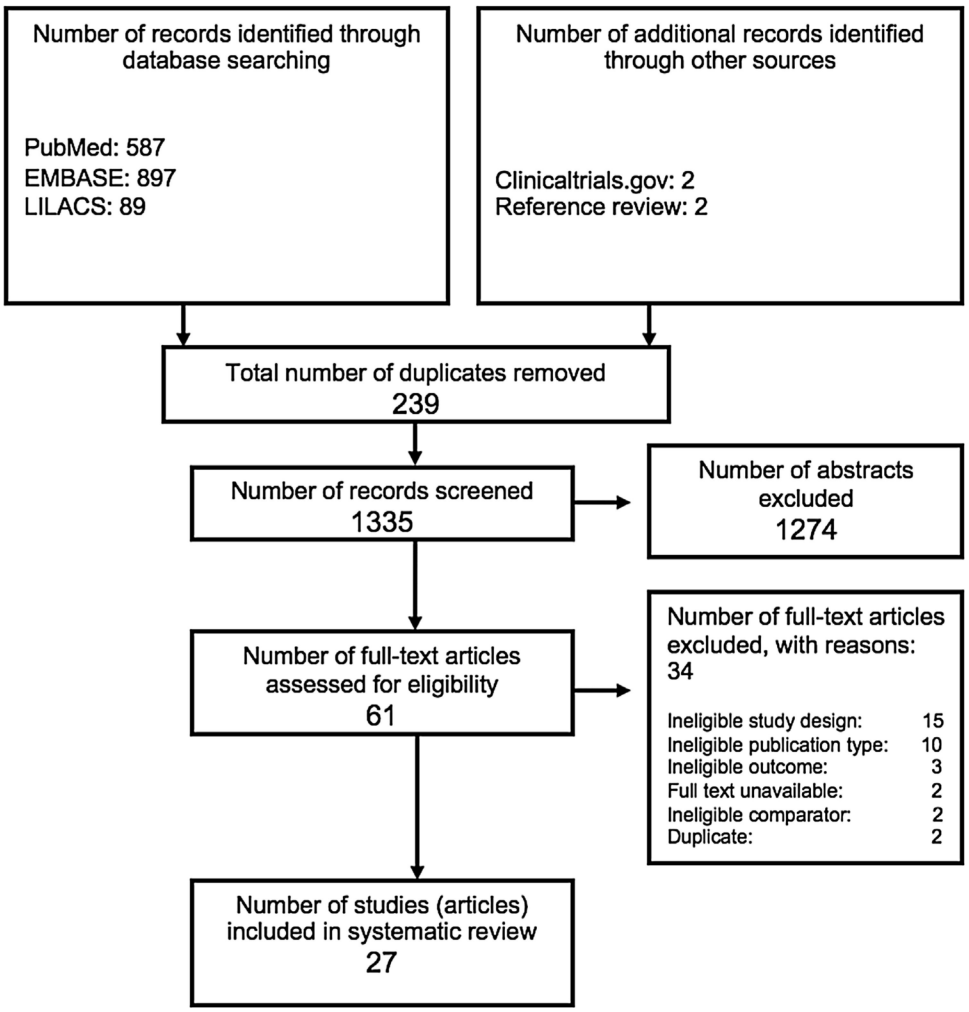

Figure 1.
PRISMA flow diagram.

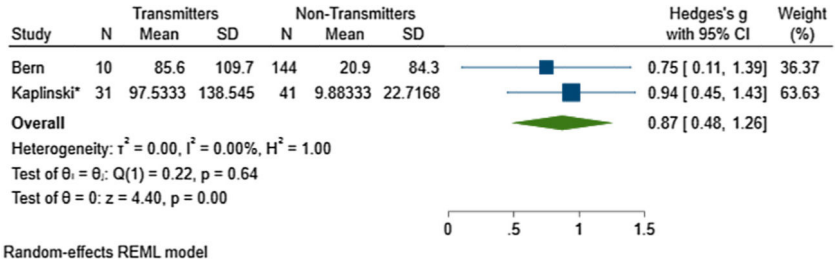

Figure 2.

Forest plot of maternal parasitic load as a risk factor for vertical transmission among **T. cruzi** seropositive mothers. *Means and standard deviations were estimated from the medians and interquartile ranges (see Methods).

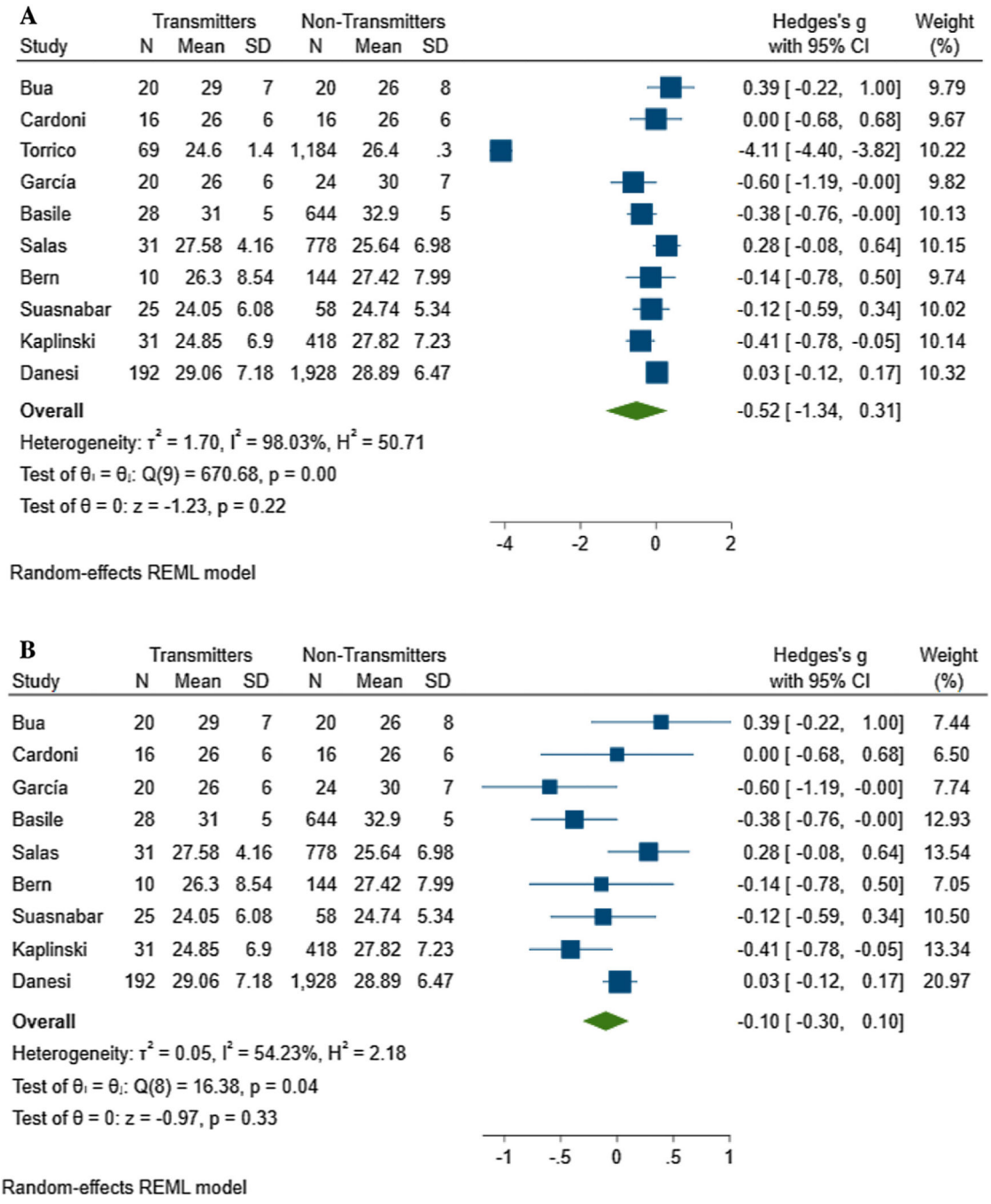

Figure 3.

Forest plots of maternal age as a risk factor for vertical transmission among **T. cruzi** seropositive mothers. A: Results from 2 studies were not included due to overlapping patient cohorts with Kaplinski et al., 2015 (Messenger et al., 2017; Rendell et al., 2015). B: Sensitivity analysis excluding Torrico et al. (2004).

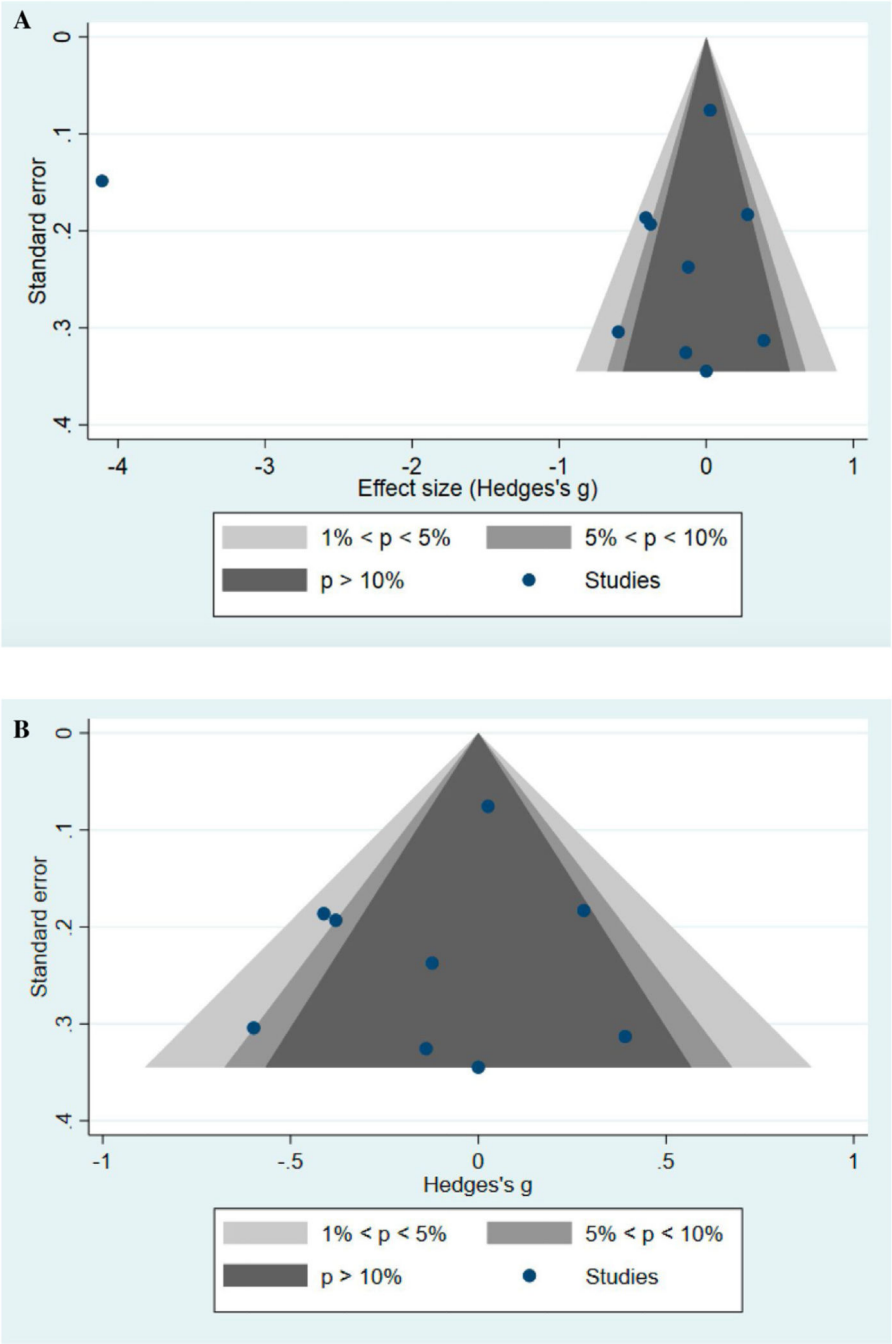

Figure 4.

Contoured funnel plot of studies examining maternal age as a risk factor for vertical transmission. A: Funnel plot of all 10 studies included in the meta-analysis of maternal age. B: Sensitivity analysis excluding Torrico et al. (2004).

Table 1

Search terms

Database	Search terms	Results (*n*)	Date searched
PubMed	("Chagas Disease"[Mesh] OR chagas[tw] OR chagas*[tw]) AND (vertical*[tw] OR congenital*[tw] OR maternal-fetal OR mother-to-child OR pregnan*[tw] OR pregnancy [mesh] OR infant, newborn[mesh] OR infant*[tw] OR feto-maternal[tw] OR Infectious Disease Transmission, Vertical[mesh]) AND (risk factors[mesh] OR risk[tw] OR risks[tw] OR risk[mesh] OR driver[tw] OR drivers[tw] OR determinant*[tw] OR predict*[tw] OR indicat*[tw] OR suscep*[tw])	587	6/19/20
EMBASE	('chagas disease' OR chagas*) AND (vertical OR 'congenital'/de OR congenital OR 'maternal fetal' OR 'mother to child' OR pregnant OR pregnancy OR 'infant'/de OR infant OR 'newborn'/de OR newborn OR 'feto maternal' OR 'pregnancy'/exp OR 'pregnancy') AND ('risk'/de OR risk OR risks OR 'driver'/de OR driver OR drivers OR 'determinant'/de OR determinant OR predict OR predictor OR indicate OR 'indicator'/de OR indicator OR susceptible OR 'susceptibility'/de OR susceptibility OR 'genetic'/de OR genetic OR 'susceptibility'/exp OR 'susceptibility')	897	6/19/20
LILACS	(chagas OR chagasic) AND (vertical OR congenital OR maternal-fetal OR mother-to-child OR pregnant OR pregnancy OR infant OR newborn OR feto-maternal) AND (risk OR risks OR driver OR drivers OR determinant OR predict OR predictor OR indicate OR indicator OR susceptible OR susceptibility)	89	6/20/20
Clinicaltrials.gov	(vertical OR congenital OR maternal-fetal OR mother-to-child OR pregnant OR pregnancy OR infant OR newborn OR feto-maternal) AND (risk OR risks OR driver OR drivers OR determinant OR predict OR predictor OR indicate OR indicator OR suscept*)|Chagas Disease	2	6/19/20

Table 2

Inclusion and exclusion criteria

PICOTSS	Inclusion criteria	Exclusion criteria
Population	Mothers with chronic Chagas disease and their infants	Mothers without confirmed serological diagnosis of *T. cruzi* infection
Exposure	Risk factors such as maternal or parasite genetics, parasitic load, living situation, socioeconomic status, maternal nutrition, etc.	Known sequelae of congenital Chagas disease (such as low birth weight or respiratory distress) or previous maternal treatment for Chagas disease
Comparison	Lack of vertical transmission of *T. cruzi* infection from a serologically positive mother to her infant	Other comparisons, such as infants of mothers without chronic Chagas disease
Outcomes	Vertical transmission of *T. cruzi* infection from a serologically positive mother to her infant	
Timing	Diagnosis of congenital Chagas disease within one year of delivery	Infant diagnosis after one year of age
Setting	Any country, medical setting, publication date, or language	
Study type	Empirical interventional or observational study designs including randomized controlled trials, cohort studies, case control studies, or cross-sectional studies	Reviews, abstracts, case studies, studies with a single case of congenital Chagas disease, letters or comments

Table 3

Evidence table of included studies.

Study	Setting	Population	Study design	Chagas prevalence and transmission rates	Diagnosis of *T. cruzi* infection in mothers and infants	Risk factors evaluated
Alonso-Vega et al. (2005)	Cochabamba, Bolivia	Mothers not infected with *T. cruzi*, mothers infected with *T. cruzi* with uninfected infants, and mothers infected with *T. cruzi* with infected infants	Case control study	Prevalence and transmission rates not available	Mother: IHA and IFA Infant: Cord blood modified micromethod or hemoculture	Compared to non-transmitting mothers, transmitting mothers were more likely to: Have lower IFN-γ (26.1 ± 10.3 pg/ml vs. 79.4 ± 27.8 pg/ml) in cells stimulated with *T. cruzi* antigen Have higher IL-10 (13.7 ± 5.3 pg/ml vs. 5.3 ± 1.6 pg/ml) in cells stimulated with *T. cruzi* antigen Produce IL-2 less frequently (7.6% vs. 35%) Have a positive hemoculture for *T. cruzi* (47% vs. 23%, $P < 0.05$)
Basile et al. (2019)	Catalonia, Spain (2010–2015)	Mothers (n = 40,084) and their infants	Surveillance study	2.8% prevalence in mothers 4.2% transmission rate	Mother: At least 2 positive serological tests Infant: Newborn micromethod, newborn PCR with confirmatory PCR at 1 month, or at least 2 positive serological tests at 9 months	Having other children with *T. cruzi* infection was significantly associated with higher odds of vertical transmission (aOR*: 22.79, 95% CI: 3.75–161.54, $P = 0.001$). Having the cardiac form of Chagas disease rather than the indeterminate form was significantly associated with higher odds of vertical transmission (aOR*: 14.4, 95% CI: 2.11–87.67, $P = 0.009$). *Adjusted for maternal age, previous treatment, clinical form of Chagas, having other children with Chagas, and time living in Catalonia. Maternal age ($P = 0.693$), country of origin ($P = 0.801$), and time living in Catalonia ($P = 0.453$) were not significantly associated with risk of vertical transmission.
Bern et al. (2009)	Santa Cruz, Bolivia (2006–2007)	Mothers (n = 530) and their infants	Surveillance study	29% prevalence in mothers 6.5% transmission rate	Mother: IHA and *Trypanosoma* Detect (InBios International) Infant: Newborn micromethod or qPCR and TESA-blot during follow-up (at least 2 positive serology results at ≥6 months required)	Mothers with PCR-positive specimens were significantly more likely to vertically transmit *T. cruzi* than mothers without PCR-positive specimens ($P = 0.012$). Transmitting mothers had significantly higher parasite loads than non-transmitting mothers (85.6 vs. 20.9 copies, $P < 0.01$). There was no significant difference in maternal age ($P = 0.64$) or parity ($P = 0.41$) between transmitting and non-transmitting mothers.
Brutus et al. (2010)	Yacuiba, Bolivia (2004–2005)	Mothers (n = 359) and their infants	Longitudinal study	40.9% prevalence in mothers	Mother: At least 2 positive serological tests (IHA and ELISA) Infant: Cord blood micromethod	Compared to non-transmitting mothers, transmitting mothers were more likely to have: Higher parasite density (26.4 ± 22.3 vs. 3.5 ± 8.4parasites/mm^3, $P < 0.001$) Parasitemia present in the third trimester of pregnancy (RR: 20.8, 95% CI: 2.6–166) There was no significant difference in parasitemia during the first or third trimester or at delivery between transmitting and non-transmitting mothers.

Study	Setting	Population	Study design	Chagas prevalence and transmission rates	Diagnosis of *T. cruzi* infection in mothers and infants	Risk factors evaluated
Bua et al. (2012)	Argentina, Bolivia, and Paraguay (2008–2011)	Mothers (n = 700) and their infants	Observational study	Prevalence and transmission rates not available	Mother: At least 2 positive serological tests (IHA, IFA, and/or ELISA) Infant: Peripheral blood micromethod at 1, 6, and 12 months, or serology	Compared to non-transmitters, transmitters were more likely to have: Parasitemia (11.0 ± 2.7 vs. 1.8 ± 0.5 eP/mL, P < 0.05) There was no significant difference in maternal age, gestational time at sampling, or *T. cruzi* serology results between transmitting and non-transmitting mothers.
Buekens et al. (2018)	Tucuman, Argentina Intibucá and Santa Bárbara, Honduras Yucatán, Mexico (2011–2013)	Mothers (n = 590,000) and their infants	Observational study	1.8% prevalence in mothers 6.6% transmission rate in Argentina 6.3% transmission rate in Mexico 0% transmission rate in Honduras	Mother: At least 2 positive serological tests (rapid antibody test and ELISA) Infant: Cord blood micromethod with qPCR, peripheral blood micromethod at 1 month, or serology at 10 months by at least two tests	Among Argentine subjects: Compared to non-transmitting mothers, transmitting mothers had a non-significant trend for higher parasitic load (median parasitic load 7.5 vs. 3.1 eP/m, P = 0.088). Among Mexican subjects: There was no significant difference in parasitic load between transmitting and non-transmitting mothers (median load 2.1 vs. 2.5 eP/mL, P = 1.00).
Burgos et al. (2007)	Buenos Aires, Argentina (2002–2006)	Infants with congenital Chagas disease (n = 47) and their mothers Unrelated seropositive pregnant women who did not transmit the infection (n = 32)	Observational study	Prevalence and transmission rates not available	Mother: At least 2 positive serological tests (IHA and ELISA) Infant: Peripheral blood micromethod in infants less than 7 months or serology by at least 2 tests in infants older than 7 months	Compared to non-transmitting mothers, transmitting mothers were more likely to have positive PCR (71.4% vs. 40.6%; no statistics provided). There was no significant difference in *T. cruzi* IId lineage between transmitting and non-transmitting mothers (P > 0.05).
Cardoni et al. (2004)	Buenos Aires, Argentina	Mothers (n = 92) and their infants	Observational study	Prevalence and transmission rates not available	Mother: At least 2 positive serological tests (IHA, IFA, ELISA, and/or DAT) Infant: Micromethod or xenodiagnosis at 1, 6, and 12 months or serology	There was no significant difference in IL-10 (26 ± 5 vs. 28 pg/ml ± 11) or IFN-γ (14 ± 3 vs. 16 pg/ml ± 3) levels between transmitting and non-transmitting mothers. There was no apparent difference in maternal age between transmitting and non-transmitting mothers (26±6 vs. 26±6; no statistics provided).
Chaparro and Genero (2018)	Chaco, Argentina (2011)	Mothers with confirmed *T. cruzi* infection (n = 247), their infants with suspected infection (n = 246), and their siblings (n = 556)	Cross sectional study	Prevalence rate not available 6.1% transmission rate	Mother: At least 2 positive serological tests (IHA and ELISA) Infant: Serology after 10 months (IHA and ELISA)	Newborn health care was associated with reduced risk of vertical transmission (aOR*: 0.21, 95% CI: 0.05–0.82, P = 0.02). Number of siblings was associated with higher odds of congenital infection (aOR†: 1.89, 95% CI: 1.43–2.49, P < 0.001). Knowledge of the infection, rural residence in infancy, living in a home with mud walls, straw roof, or dirt floor, triatomine bugs in the home, blood transfusions, maternal diagnosis of *T. cruzi* infection, annual cardiology care, and household cohabitants were not associated with odds of congenital transmission. *Adjusted for knowledge of the infection, rural residence in infancy, living on a farm, triatomine bugs in the home, blood transfusions, maternal diagnosis of *T. cruzi* infection, annual cardiology care, and household cohabitants. †Adjusted for knowledge of the infection, rural residence in infancy, living on a farm, triatomine bugs in the home, blood

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Study	Setting	Population	Study design	Chagas prevalence and transmission rates	Diagnosis of *T. cruzi* infection in mothers and infants	Risk factors evaluated
						transfusions, maternal diagnosis of *T. cruzi* infection, annual cardiology care, and evaluation for Chagas among siblings.
Danesi et al. (2020)	Buenos Aires, Sante Fe, and Salta, Argentina (2002–2015)	Children and their mothers (n = 2120)	Retrospective cohort study	Prevalence rate not available 9% transmission rate	Mother: not specified; identified in retrospective cohort Infant: History of positive parasitological tests or two reactive serological tests after 10 months	Children with an infected sibling were significantly more likely to be congenitally infected than children without an infected sibling (RR=4.4, 95% CI: 2.3–8.4). Children from null to low endemicity areas were significantly more likely to be congenitally infected than children from medium to high endemicity areas (11.1% vs. 8.2%, P = 0.033). Children with a maternal grandmother infected with *T. cruzi* were significantly more likely to be congenitally infected than children without an infected maternal grandmother (13.9% vs. 7.2%, P = 0.001). There was no significant difference in maternal age between transmitting and non-transmitting mothers (P = 0.7389).
García et al. (2008)	Argentina	Women (n = 116) and their infants	Observational study	Prevalence and transmission rates not available	Mother: At least 2 positive serological tests (IHA, IFA, and/or ELISA) Infant: Micromethod at delivery, 1 month, or 6 months	Compared to non-transmitting mothers, transmitting mothers had significantly lower TNF and sTNF-R1 values (P < 0.05 for both). There was no apparent difference in maternal age between transmitting and non-transmitting mothers (26 ± 6 vs. 30± 7); no statistics provided. There was no significant difference in percentage of monocytes, sTNF-R2, or IL-10 between transmitting and non-transmitting mothers. At 1 month of age, infected infants had significantly lower levels of TNF than non-infected infants (P < 0.05); there was no difference at 6 or 12 months of age. At 1 and 12 months of age, infected infants had significantly higher levels of sTNF-R2 than uninfected infants; there was no difference at 6 months of age. There was no significant difference in IL-10 or sTNF-R1 levels between infected or uninfected infants at 1, 6, or 12 months of age.
Hermann et al. (2004)	Cochabamba, Bolivia	Pregnant women with confirmed *T. cruzi* infection who did (n = 24) and did not (n = 35) transmit to their infants	Prospective cohort study	Prevalence and transmission rates not available	Mother: Serology (not specified) Infant: Micromethod or hemoculture, with negative results confirmed by PCR	Compared to non-transmitting mothers, transmitting mothers: Were more likely to have positive hemoculture results (47.4% vs. 26.3%, P < 0.05) Had higher levels of IFN-γ (P < 0.01) Had lower proportions of CD4+ HLA-DR+ T lymphocytes (P < 0.05) There were no significant differences in IL-2, IL-4, IL-10, TGF-β1, or proportions of CD4+ CD45RO+ T cells between transmitting and non-transmitting mothers.
Herrera et al. (2019)	Tucuman, Argentina Intibucá, Honduras Santa Bárbara, Honduras	Mothers with T *cruzi* infection (n = 100) and their infants	Nested prospective cohort study	Prevalence and transmission rates not available	Mother: At least 2 positive serological (rapid test and/or ELISA) or PCR tests Infant: Not specified	*T. cruzi* haplotypes differed significantly between transmitting and non-transmitting cases (P = 0.021). In particular, the non-TcI-H1 haplotype was more common in transmitting than non-transmitting cases.

Study	Setting	Population	Study design	Chagas prevalence and transmission rates	Diagnosis of *T. cruzi* infection in mothers and infants	Risk factors evaluated
	Merida, Mexico Valladolid, Mexico					
Juiz et al. (2016)	Argentina, Bolivia, and Paraguay	*T. cruzi* seropositive mothers and their infants (n = 217)	Case control study	Prevalence rate not available 4.7% transmission rate	Mother: Serology (not specified) Infant: Micromethod in infants less than 6 months or serology by at least 2 tests after 9 months	Other SNPs in ALPP (rs2014683 and rs1048988), MMP2 (rs243865, rs243864, and rs2285053), and MMP9 (rs3919242 and rs2234681) were not associated with transmission. *Adjusted for all other SNPs in the analysis and sex
Kaplinski et al. (2015)	Santa Cruz and Camiri, Bolivia (2010–2013)	Pregnant women (n = 1696) and their infants	Prospective cohort study	26.9% prevalence in mothers 6.8% transmission rate	Mother: At least 2 positive tests (*Trypanosoma* Detect [InBios, Seattle, WA], IHA, and/or ELISA) Infant: Micromethod at deliveryor 1 month, or serology at 6- or 9-month follow-up (IgM TESA-blot confirmed by IHA or ELISA)	Compared to non-transmitting mothers, transmitting mothers: Had significantly higher parasite loads (median load 62 vs. 0.05 parasite equivalents/mL, $P < 0.0001$) Were significantly more likely to have positive T. cruzi PCR results ($P < 0.0001$) Were significantly younger (median age 24.0 vs. 26.8 years, $P = 0.04$) Were significantly more likely to have had a twin birth ($P = 0.04$) Were significantly less likely to have ever lived in a house infested with triatomine bugs ($P = 0.04$) Were significantly less likely to ever live in a house with mud walls ($P = 0.04$) Spent significantly fewer years living in an infested house ($P = 0.02$) or house with mud walls ($P = 0.02$) Likelihood of having a Cesarean section, parity, living in a rural area, currently living in an infested house, living in a house with an earth floor, completing secondary school, and home appliances owned were not significantly different between transmitting and non-transmitting mothers.
Messenger et al. (2017)	Santa Cruz, Bolivia (2010–2014)	Pregnant women (n = 1851) and their infants	Prospective cohort study	25.7% prevalence in mothers 7.8% transmission rate	Mother: At least 2 positive tests (Trypanosoma Detect or Chagas Detect Plus [InBios, Seattle, WA], IHA, and/or ELISA) Infant: qPCR by at least two tests or micromethod as newborns or at 1-, 6-, or 9-month follow-up, or serology (IgM TESA-blot, IHA, or ELISA) at 6- or 9-month follow-up	Compared to non-transmitters mothers, transmitting mothers were significantly younger (median age 23.5 vs. 26.9 years, $P < 0.01$). Female infants were significantly more likely to be congenitally infected than male infants ($P < 0.05$).
Murcia et al. (2013)	Murcia, Spain (2007–2011)	*T. cruzi* seropositive women (n = 59) and their infants	Observational study	Prevalence rate not available 13.8% transmission rate	Mother: At least 2 positive tests (IFA and ELISA) Infant: PCR or hemoculture at 0–2, 6, 9, or 12 months, or serology that remained positive at 12 months	Seropositive mothers with a positive *T. cruzi* PCR result during pregnancy were more likely to vertically transmit the infection than seropositive mothers with a negative PCR result ($P = 0.0046$).
Murcia et al. (2017)	Murcia, Spain (2007–2016)	*T. cruzi* seropositive women (n = 144) and their infants (n = 160)	Observational study	Prevalence rate not available 10% transmission rate	Mother: 2 serological tests (chemiluminescent microparticle immunoassay [Architect $i2000_{SR}$ Immunoassay, Abbott, IL] and IFA) Infant: PCR or micromethod in	Mothers with a positive *T. cruzi* PCR result were more likely to vertically transmit than mothers with a negative PCR result (18.8% vs. 0%; $P = 0.0001$).

Study	Setting	Population	Study design	Chagas prevalence and transmission rates	Diagnosis of *T. cruzi* infection in mothers and infants	Risk factors evaluated
					infants, or serology that remained positive at12 months	
Rendell et al. (2015)	Santa Cruz, Bolivia (2010–2011)	Pregnant women (n = 596) and their infants	Prospective cohort study	21.5% seroprevalence in mothers 11.7% transmission rate	Mother: At least 2 tests (TrypanosomaDetect [InBios, Seattle, WA], IHA, and/or ELISA) Infant: Micromethod (timing not specified), positive serology at 6 months with ELISA absorbance value >0.7 or any positive serology at 9 months, positive PCR in at least 2 samples, or positive PCR plus positive IgM TESA-blot	Compared to non-transmitting mothers, transmitting mothers were significantly more likely to have twin births than singleton births (P = 0.03). Congenital transmission occurred in 31.3%, 15.4%, and 0% of women with high, moderate, and low parasite loads, respectively (χ^2 for trend 18.2, P < 0.0001). Women who reported living in an infested house for 1–19 years or 20 or more years had lower odds of congenital transmission than women with 0 years of living in an infected house (P = 0.049). Congenital transmission occurred in 16.1%, 13.3%, and 0% of women who lived in an infested house for 0, 1–19, or 20 or more years, respectively (P = 0.049). Maternal age (P = 0.92), ever living in an infested house (0.28), and currently living in an infested house (P = 0.46) were not significantly associated with odds of congenital transmission.
Salas et al. (2007)	Yacuiba, Bolivia (2003–2005)	Pregnant women (n = 2712) and their infants (n = 2742)	Observational study	42.2% seroprevalence in mothers 5.1% transmission rate	Mother: At least 2 positive serological tests (IHA and ELISA) Infant: Cord blood micromethod at delivery or peripheral blood micromethod at 1 month	Among all mothers (with and without Chagas disease), positive maternal T. cruzi serology (aOR*: 19.39, P < 0.0001, 95% CI: 5.95–62.71) and positive maternal parasitemia (aOR: 11.62*, P < 0.0001, 95% CI: 5.92–22.82) were associated with higher odds of vertical transmission. Among all mothers (with and without Chagas disease), maternal age, parity, time of residence, being born in Yacuiba, living in a rural area, being without an insecticide house-spraying program, lack of antenatal visit, Cesarean section, infant sex, hot season of delivery, and previous stillbirth were not significantly associated with odds of transmission (P > 0.05). Congenital transmission rate was not significantly different between singleton and twin births (P = 0.12). Congenital transmission was more common among infants from multiple pregnancies than in singletons (13.5% vs. 2.6%, χ2= 11.51, P < 0.01). *Adjusted for maternal age over 30, giving birth during the hot season (July to February), positive maternal parasitemia, and positive maternal serology.
Negrette et al. (2005)	Salta, Argentina (1997–2002)	Children (n = 340) born to *T. cruzi* seropositive mothers	Observational study	Prevalence rate not available 9.1% transmission rate	Mother: IHA or ELISA Infant: Serology after 8 months and confirmed at ~12 months	Mothers from endemic regions with low vector control were significantly less likely to vertically transmit the infection than mothers from endemic regions with high vector control (P = 0.045). Maternal age, infant sex, and sibling order were not significantly associated with risk of congenital infection.
Scapellato et al. (2009)	Buenos Aires, Argentina (2001–2007)	Infants (n = 94) born to *T. cruzi* seropositive mothers	Observational study	Prevalence rate not available	Mother: At least 2 positive tests (IHA, ELISA, and/or latex agglutination)	Compared to non-transmitting mothers, transmitting mothers were more likely to have HIV (100% vs. 10.9%, P = 0.0021).

Study	Setting	Population	Study design	Chagas prevalence and transmission rates	Diagnosis of *T. cruzi* infection in mothers and infants	Risk factors evaluated
				13.8% transmission rate	Infant: Micromethod at 3 visits before 6 months or serology by at least 2 tests after 6 months	
Suasnabar et al. (2018)	Santa Fe, Argentina (1990–2017)	Women (n = 83) and infants (n = 237) with confirmed *T. cruzi* infections	Retrospective cohort study	Prevalence and transmission rates not available	Mother: At least 2 positive serological tests (IHA, IIF with DA, and/or ELISA) Infant: Parasitology (xenodiagnosis or Strout) in the first months of life or serology by at least 2 tests after 10 months	Mothers with medium or high vector exposure had significantly lower risk of vertical transmission than mothers with no or low vector exposure (RR = 0.36, 95% CI: 0.14–0.97, P = 0.046). Compared to non-transmitting mothers, transmitting mothers were significantly more likely to have a positive xenodiagnosis, controlled for maternal age, transfusion history, and maternal vector exposure (RR= 12, 95% CI: 2.9–50.1). Maternal age and history of transfusion were not significantly associated with risk of vertical transmission (P = 0.059 and 0.605, respectively).
Torrico et al. (2004)	Cochabamba, Bolivia (1992–1994; 1999–2001)	Two cohorts of infants and their mothers Cohort A: n = 1606 infants; Cohort B: n = 3879 mothers)	Observational study	Prevalence in mothers: Cohort A: 27.6% Cohort B: 17.3% Transmission rate: Cohort A: 4.9% Cohort B: 5.9%	Mother: IHA and/or immunofluorescence Infant: Micromethod or hemoculture from cord blood or peripheral blood within 1 month	Compared to non-transmitting mothers, transmitting mothers were: Younger (23.7 ± 0.7 vs. 26.4 ± 0.3 years, P < 0.05)* Had lower parity (1.8 ± 0.2 vs. 2.6 ± 0.1; P < 0.05)* There was no significant difference in sex ratio between congenitally infected and uninfected infants (cohort A: 54.6% vs. 51.6% male infants; cohort B: 63.3% vs. 49.5% male infants). *Adjusted for maternal age, parity, abortion history, and premature rupture of membranes.
Torrico et al. (2005)	Cochabamba, Bolivia (1992–1994; 1999–2001)	Two cohorts of infants and their mothers (Cohort A: n = 1954 infants; Cohort B: n = 5775 mothers)	Observational study	19.9% prevalence in mothers 4.6% transmission rate	Mother: IHA and IFA Infant: Micromethod, hemoculture, or PCR using cord blood or peripheral blood at 1 month	Compared to non-transmitting mothers, transmitting mothers were significantly more likely to have premature rupture of membranes (40.8% vs. 11.7%, P < 0.001).* There was no significant difference in vertical transmission rates among mothers from low, medium, or high endemicity areas (P > 0.05).* There was no significant difference in percent of female infants between congenitally infected and uninfected infants (39.4% vs. 46.7%, statistics not provided).* There was no apparent difference in maternal age between transmitting and non-transmitting mothers (23.6 ± 0.7 vs. 24.5 ±0.2; statistics not provided).* There was no apparent difference in parity, history of abortions, BMI, or hematocrit between transmitting and non-transmitting mothers (statistics not provided).* *The study did not specify whether non-transmitting mothers only included T. cruzi seropositive women.
Torrico et al. (2006)	Cochabamba, Bolivia (1992–1994; 1999–2001)	*T. cruzi* seropositive mothers (n = 801) and their infants	Observational study	Prevalence and transmission rates not available	Mother: IHA and/or IFA Infant: Micromethod from cord blood or peripheral blood before 1 month or hemoculture, with negative results confirmed by PCR	Compared to non-transmitting mothers, transmitting mothers were: Younger (23.7 ± 0.7 vs. 26.4 ± 0.2 years; P < 0.05) Had a lower number of previous pregnancies (2.7 ± 0.2 vs. 3.5 ± 0.2 pregnancies; P < 0.05) There was no significant difference in blood hematocrit

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Study	Setting	Population	Study design	Chagas prevalence and transmission rates	Diagnosis of *T. cruzi* infection in mothers and infants	Risk factors evaluated
						or hemoglobin levels between transmitting and non-transmitting mothers (statistics not provided).
Volta et al. (2016)	Buenos Aires, Argentina (2008–2011)	Congenitally infected infants (n = 35), uninfected infants born to *T. cruzi* seropositive mothers (n = 10), and uninfected infants born to *T. cruzi* seronegative mothers (n = 10)	Retrospective cohort study	Prevalence and transmission rates not available	Mother: Serology (not specified) Infant: Micromethod within 1 month or at 6 months or serology from 10–12 months	Compared to uninfected infants of *T. cruzi* seropositive mothers, congenitally infected infants had significantly: Higher plasma levels of IL-17A, MCP-1, and MIG Lower levels of IFN-γ (P < 0.0001) Congenitally infected infants diagnosed after 6 months had significantly higher plasma levels of IL-6 and IL-17F at 1 month of age than uninfected infants.

Abbreviations: IHA: indirect hemagglutination IFA: indirect immunofluorescence assay ELISA: enzyme-linked immunosorbent assay DAT: direct agglutination test IIF: Indirect Immunofluorescence DA: Direct Agglutination with 2-merceptoethanol.

Table 4

Summary of evidence by risk factor.

Risk factor	Studies suggesting increased risk of vertical transmission	Studies suggesting no difference in risk of vertical transmission
Maternal age	Three studies found an increased risk among younger mothers (Kaplinski et al., 2015; Messenger et al., 2017; Torrico et al., 2004).	Ten studies found no significant difference in risk with maternal age (Basile et al., 2019; Bern et al., 2009; Bua et al., 2012; Cardoni et al., 2004; Danesi et al., 2020; García et al., 2008; Martin Suasnabar et al., 2018; Negrette et al., 2005; Rendell et al., 2015; Salas et al., 2007).
Maternal parity	One study found an increased risk in infants with a larger number of siblings (Chaparro and Genero, 2018).	Two studies found significant no difference in risk with maternal parity (Bern et al., 2009; Salas et al., 2007).
Parasite load and diagnostics	Several studies found an increased risk with parasite load (Bern et al., 2009; Brutus et al., 2010; Bua et al., 2012; Kaplinski et al., 2015; Rendell et al., 2015), positive parasitemia (Salas et al., 2007), positive PCR (Bern et al., 2009; Burgos et al., 2007; Murcia et al., 2017, 2013), * positive *T. cruzi* hemoculture (Alonso-Vega et al., 2005; Hermann et al., 2004), or positive xenodiagnoses during pregnancy (Martin Suasnabar et al., 2018).	One study found a non-significant trend for higher risk with parasitic load among one subpopulation and no difference in risk in another subpopulation (Buekens et al., 2018).
Parasite genetics	One study found apparent clustering of parasite sequences from congenital transmission cases in the TcII-TcV-TcVI cluster (Herrera et al., 2019). *	One study found no significant difference in risk with *T. cruzi* IId lineage (Burgos et al., 2007).
Infant genetics	One study found an increased risk with infant mutations in SNPs of the *ADAM12* (rs11244787, rs1871054) and *MMP2* (rs243866, rs17859821, rs2285053) genes, which code for placental expression enzyme (Juiz et al., 2016).	One study found no significant difference in risk with infant mutations in SNPs of the *ALPP* (rs2014683, rs1048988), *MMP2* (rs243865, rs243864, rs2285053), and *MMP9* (rs3919242, rs2234681) genes (Juiz et al., 2016).
Socioeconomic factors		Two studies found no significant difference in risk among women who lived in a rural area (Salas et al., 2007) or lived in a rural area during infancy (Chaparro and Genero, 2018). One study found no significant difference in risk among women based on home construction materials, education level, types of appliances owned, or living in a rural area (Kaplinski et al., 2015).
Twins	Two studies found higher risk in twin than singleton births (Kaplinski et al., 2015; Rendell et al., 2015).	One study found no significant difference in risk between twin and singleton births (Salas et al., 2007).
Siblings and families	One study found an increased risk with having other siblings with Chagas (Basile et al., 2019). One study found an increased risk among infants whose maternal grandmother was infected with *T. cruzi* (Danesi et al., 2020). It also found an increased risk among infants with siblings infected congenitally.	
Immunologic factors	One study found an increased risk among infants with higher IL-17A, higher MCP-1, higher monokine induced by IFN-γ, and lower IFN-γ (Volta et al., 2016).	One study found no significant difference in risk by maternal IL-2, IL-4, IL-10, or TGF-β1 levels (Hermann et al., 2004).
	One study found an increased risk among women whose cord blood had higher IFN-γ and lower IL-10 (Alonso-Vega et al., 2005). *	One study found no significant difference in risk by maternal IL-10 or IFN-γ levels (Cardoni et al., 2004).
	One study found increased risk among women with higher IFN-γ in whole blood cells incubated with *T. cruzi* lysate and women with lower proportions of $CD4^+$ $HLA\text{-}DR^+$ T lymphocytes (Hermann et al., 2004).	One study found no significant difference in risk by blood leukocyte count, percentage of monocytes, levels of sTNF-R2, or levels of IL-10 (García et al., 2008).
	One study found an increased risk among mothers with lower TNF-α levels (Cardoni et al., 2004). *	One study found no significant difference in risk by infant levels of IL-10 or sTNF-R1 (García et al., 2008).

Risk factor	Studies suggesting increased risk of vertical transmission	Studies suggesting no difference in risk of vertical transmission
	One study found an increased risk among mothers with lower TNF and sTNF-R1 (García et al., 2008).	
	One study found an increased risk among infants with lower levels of TNF at 1 month or higher levels of sTNF-R2 at 1 and 12 months (García et al., 2008).	
Maternal HIV status	One study found an increased risk among women with HIV (Scapellato et al., 2009).	
Vector exposure	Two studies found a higher risk among women who had never lived in a triatomine-infested house than women who had (Kaplinski et al., 2015; Rendell et al., 2015).	Three studies found no significant difference in risk between women who reported currently having triatomine bugs in the home and women who did not (Chaparro and Genero, 2018; Kaplinski et al., 2015; Rendell et al., 2015).
	One study found a higher risk among women with low or no vector exposure than women with medium or high vector exposure (Martin Suasnabar et al., 2018).	
	One study found a higher risk among women from endemic areas with high vector control than women from endemic areas with low vector control (Negrette et al., 2005).	
	One study found a higher risk among women from areas of low vectorial risk than high vectorial risk (Danesi et al., 2020).	
Infant sex	One study found an increased risk among female infants (Messenger et al., 2017).	Two studies found that infant sex was not a significant risk factor (Negrette et al., 2005; Salas et al., 2007; Torrico et al., 2004).
Other	One study found increased risk with the maternal cardiac form of Chagas disease, compared to the indeterminate form (Basile et al., 2019).	Two studies found that maternal history of blood transfusion was not a significant risk factor (Chaparro and Genero, 2018; Martin Suasnabar et al., 2018).
		One study found that sibling order was not a risk factor (Negrette et al., 2005).
		One study found no significant difference in risk by maternal hemoglobin or hematocrit levels (Torrico et al., 2006). *

* Statistics not provided in the original study for this association

Table 5

Parasitic loads of transmitting and non-transmitting *T. cruzi* seropositive mothers. Data from Rendell and colleagues are not reported here due to overlapping data with Kaplinski and colleagues (Kaplinski et al., 2015; Rendell et al., 2015).

Study	Transmitting mothers		Non-transmitting mothers		Reported statistic	Method
	N	Parasitic load (mean ± standard deviation)	*N*	Parasitic load (mean ± standard deviation)		
Bern et al., 2009	10	85.6 ± 109.7 eP/mL	144	20.9 ± 84.3 eP/mL	$P < 0.01$	qPCR with primer set Cruzi 1 and Cruzi 2
Kaplinski et al., 2015 *	31	97.5 ± 138.5 eP/mL	41	9.9 ± 22.7 eP/mL	$P < 0.0001$	qPCR with primer set Cruzi 1 and Cruzi 2
Bua et al., 2012	20	11 ± 2.7 eP/mL	20	1.8 ± 0.5 eP/mL	$P < 0.05$	SYBR GreenER qPCR SuperMix Universal kit
Buekens et al., 2018	11	8.6 ± 11.8 eP/mL	336	5.7 ± 7.4 eP/mL	–	qPCR with primer sets Tcz1-Tcz2 and 121–122
Brutus et al., 2010 †	–	26.4 ± 22.3 p/mm^3	–	3.5 ± 8.4 p/mm^3	$P = 0.001$	Microscopic examination of parasites in buffy coat of heparinized microhematocrit tubes

eP/mL: equivalent parasites per milliliter. p/mm^3: parasites per cubic millimeter.

* Means and standard deviations were estimated from the medians and interquartile ranges (See Methods).

† This study included 147 *T. cruzi* seropositive mothers but did not report the number of transmitting and non-transmitting women.