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Congenital Chagas disease: progress toward implementation of pregnancy-based screening

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Abstract

Purpose of review—Lack of recognition of congenital Chagas disease in infants of mothers from endemic regions who are living in countries nonendemic for *Trypanosoma cruzi* infection suggests a high rate of underdiagnosis. Pregnancy is the optimal access point for identifying Chagas disease in at-risk mothers and their infants. In this review, we update progress toward implementation of pregnancy-based screening for congenital Chagas disease in nonendemic settings.

Recent findings—International organizations have updated recommendations for diagnosis, treatment and prevention of congenital Chagas disease. Reports of successful implementation of pregnancy-based screening at some centers provide a model for optimizing diagnosis of congenital Chagas disease. Screening family members of index patients may identify additional *T. cruzi*-infected persons. Promising tests to augment current diagnostic modalities for maternal and congenital Chagas disease are in development. Universal or risk-based screening would be cost-effective. More healthcare providers are now aware that treatment of congenital Chagas disease is curative and are promoting efforts to make pregnancy-based screening for congenital Chagas disease a standard of care.

Summary—Ongoing efforts to implement routine pregnancy-based screening for congenital Chagas disease in nonendemic regions will mutually benefit infants, their mothers and family members and can prevent potentially fatal Chagas cardiomyopathy.

Keywords

congenital Chagas disease; pregnancy-based screening; *Trypanosoma cruzi* infection

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INTRODUCTION

Chagas disease is a vector-borne zoonosis with many mammalian reservoirs caused by the protozoan parasite, *Trypanosoma cruzi*. Chagas disease is endemic in Mexico, Central America and South America. The triatomine bug, often known as a 'kissing bug', is the vector for Chagas disease. Vector species acquire infection by biting an animal or person already infected with *T. cruzi*. Triatomines defecate during or after taking a blood meal and transmission occurs when a susceptible host rubs infected fecal material into a bite site or onto mucous membranes. Transmission can also occur through transfusion of blood or transplant of organs from infected donors, by consumption of foods contaminated by vector feces or congenitally.

Programs in endemic regions to limit vectorial spread of Chagas disease have been extremely successful. The current global Chagas disease burden estimate is 6 million persons with infection and 1.2 million with Chagas cardiomyopathy [1■■]. As vectorial transmission has declined, the proportion of disease attributable to other routes has increased and an estimated 22.5% of incident infections now occur through congenital transmission [2]. In a recent meta-analysis, the pooled rate of congenital transmission was 4.7% [3].

Acute Chagas disease acquired by vector-mediated transmission is usually a mild illness or asymptomatic infection lasting several weeks. Infection then enters a chronic phase that, without antitrypanosomal treatment, persists for life. Twenty to 30% of those with chronic Chagas disease progress over years or decades to a determinate form, usually manifesting as cardiomyopathy but occasionally as mega-syndromes of the esophagus or colon. Chagas cardiomyopathy results from chronic inflammation that involves all chambers of the heart and damages the conduction system. The pathogenesis involves parasite persistence in cardiac tissue and immune-mediated myocardial injury. Early cardiomyopathy usually presents as conduction system abnormalities, especially right bundle branch block or segmental left ventricular wall motion abnormalities. Later manifestations include ventricular arrhythmias, complete heart block, apical aneurysm and thromboemboli, each of which can be fatal, as well as progressive heart failure [1■■].

Congenital Chagas disease is acute-phase disease in the newborn. Many affected newborn infants are asymptomatic. Approximately 10–40% have clinical signs of congenital infection, such as prematurity, hepatosplenomegaly and thrombocytopenia, but none is specific for Chagas disease. All infants with missed congenital Chagas disease are at risk for later development of potentially fatal Chagas cardiomyopathy, as are their mothers and infected family members. Implementation of pregnancy-based screening would allow provision of curative treatment to affected infants and, potentially, for their mothers and family members [4]. This review summarizes recent progress toward implementation of pregnancy-based Chagas disease screening in at-risk women with an emphasis upon those residing in nonendemic countries, where need for these programs is great.

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UPDATED RECOMMENDATIONS FOR DIAGNOSIS, TREATMENT AND PREVENTION OF CONGENITAL CHAGAS DISEASE

Updated recommendations of the WHO Technical Group, 'Prevention and Control of Congenital Transmission and Case Management of Congenital Infections with *Trypanosoma cruzi*' in 2019 estimated that there are 1,125 000 women of childbearing age in Latin America with Chagas disease and that an estimated 8668 infants with congenital Chagas disease are born yearly in Latin America. There is increasing recognition that, due to migration from Latin America, congenital Chagas disease has become a global concern. Congenital Chagas disease is reported in infants born in several European countries as well as Canada, the United States and Japan [5].The WHO recommends focusing on five population groups within or outside of Latin America to eliminate congenital transmission of *T. cruzi*: girls and female adolescents; nonpregnant women; pregnant women by antenatal screening; neonates born to infected mothers and relatives and other children born to infected mothers. Mothers with Chagas disease should receive treatment after delivery and completion of breastfeeding to prevent transmission during subsequent pregnancies. Infants should have evaluation for congenital infection and all infants with congenital Chagas disease should receive treatment.

The Pan American Health Organization has endorsed a framework for elimination of mother-to-child transmission of HIV, syphilis, hepatitis B and Chagas disease. The aim for Chagas disease is cure of greater than 90% of children with congenital infection. The framework describes how to incorporate serological screening for Chagas disease when screening for HIV, syphilis and hepatitis B during pregnancy and monitoring *T. cruzi*-positive women during pregnancy to organize their treatment and diagnosis and treatment of the newborn [6].

The US Centers for Disease Control and Prevention (CDC) recommends that women at risk for Chagas disease undergo screening for infection before or during pregnancy and notes that women who have lived in Mexico, Central America and South America are at greatest risk for Chagas disease [7]. Targeted maternal screening would enable early identification and treatment of at-risk infants, but antenatal screening for *T. cruzi* is not yet the standard of care in the United States [4].

RISK-BASED SCREENING IN NONENDEMIC SETTINGS

Catalonia, in northeast Spain, implemented comprehensive public health surveillance for congenital Chagas disease in 2010 and reported findings for the program's first 6 years in 2019 [8■■]. Approximately 6% of the population, or 450 000 of the region's 7.5 million inhabitants, were born in countries where Chagas disease is endemic. Maternal screening rates increased from 68 to 89% during the program. Overall, 33 469 pregnant women were tested for antibody to *T. cruzi* and 937 were confirmed as positive for infection by screening and subsequent confirmatory testing using different antigens or serological techniques. The overall prevalence was 2.8 positive cases per 100 pregnancies tested with the highest rates in women from Bolivia (15.8%), El Salvador (1.4%) and Paraguay (1.2%).

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During the 6 years reported, 90% of newborns had parasitological testing at birth by microhematocrit (58%) or *T. cruzi* PCR (87%). Those with a positive PCR had a confirmatory test 4 weeks later. Overall, 83% of newborns completed serological testing at 9–12 months of age. Twenty-eight infants had congenital Chagas disease (4.2%). Four had signs consistent with Chagas disease, including hepatomegaly, splenomegaly and jaundice. All infants received treatment with benznidazole. This comprehensive approach illustrates many of the features key to success of a maternal screening program (Table 1).

In Europe, Italy and Spain are countries with high numbers of migrants from Latin America. Among the approximately 3268–5015 *T. cruzi*-infected individuals living in Italy, an estimated 463 live births occurred to women with Chagas disease during 2014–2018 [9]. Pregnancy-based screening of Bolivian women for Chagas disease was systematically conducted from 2014 through 2016 in all hospitals in Bergamo province in Northern Italy that offered antenatal and delivery care [10]. Twenty-eight of 376 Bolivian women had confirmed Chagas disease for a prevalence of 8.7% [95% confidence interval (CI), 0–12.6]. Among 22 infants evaluated at birth and until 9 months of age, one infant had congenital Chagas disease and received appropriate treatment.

Systematic screening of pregnant women from endemic areas at three tertiary hospitals in Madrid (2012–2016) identified 122 women with Chagas disease from Bolivia (81%), Paraguay (12%), Argentina (2%) and Honduras (2%). Vertical transmission occurred in three of 109 infants who completed 12 months of follow-up. The infected infants were PCR positive at birth and 1 month of age. The single symptomatic infant had hydrops fetalis [11]. The mean age at which uninfected infants had negative serology was 10.5 months.

In the United States, an estimated 238 091 persons have *T. cruzi* infection before inclusion of undocumented migrants, who may account for as many as 109 000 additional cases [12]. One US-based study assessed the feasibility of screening women from a Chagas-endemic region during the postpartum period using a point-of-care test (Chagas Detect Plus; InBios International, Inc., Seattle, Washington, USA). Although initial screening of 138 women, most of whom cited Mexico (47%), Guatemala (21%) or Honduras (13%) as their birth country, found 16.7% were positive, confirmatory testing was negative for all patients [13].

SCREENING FAMILY MEMBERS

Screening family members of index patients with Chagas disease is an important public health intervention. One such study, conducted in Chile, evaluated family members of 70 women confirmed to have Chagas disease during pregnancy. Six newborn infants had congenital Chagas disease (8.6%). In addition, 10 of 57 (18%) children of the index mothers, 57 of their own mothers (81%) and 75 of 152 maternal siblings (49%) were infected by *T. cruzi* [14]. Although the contribution of vector-mediated and other modes of transmission in endemic regions is difficult to assess, there were clear benefits of testing family members in this setting.

Available evidence supports the premise that diagnosis of Chagas disease in pregnant women living in a nonendemic region should prompt screening their other children, parents

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and siblings. In the active surveillance conducted in Catalonia [8■■], 178 previous children of index mothers were screened and 14 (7.8%) had *T. cruzi* infection. In the United States, screening of 189 relatives of 86 Chagas disease patients confirmed *T. cruzi* infection in 14 (7.4%) [15]. Four were children of index patient mothers and seven were siblings. In Canada, a 34-year-old woman, upon learning her mother had Chagas disease, requested testing. She and two of her siblings, all born and raised in Canada, had *T. cruzi* infection [16]. A report of 60 patients with Chagas disease managed in hospitals throughout New York City noted that five were US born to immigrant parents, suggesting mother-to-child transmission in a nonendemic country [17].

TESTS FOR MATERNAL AND CONGENITAL CHAGAS DISEASE DIAGNOSIS

Serologic screening during pregnancy follows country-specific protocols. For example, in Italy a chemiluminescent immunoassay (ChLIA, ABBOTT PRISM Chagas) is in use for initial screening. For specimens with a positive result, a more specific technique (chemiluminescent microparticle immunoassay, CMIA, ABBOTT ARCHITECT Chagas) is employed [10].

In the United States, there are four FDA-cleared diagnostic tests for *T. cruzi* IgG [18]. Of these four diagnostic tests, the ORTHO *T. cruzi* ELISA Test System (Ortho Clinical Diagnostics, Raritan, New Jersey, USA) is available only for blood donor screening and the InBios Chagas Detect *Plus* Rapid Test (InBios International Inc., Seattle, Washington, USA) is a point-of-care test. Whitman *et al.* [19■] evaluated the performance of the two tests currently available at commercial laboratories using 500 seropositive and 300 seronegative blood donor plasma samples. The Wiener Chagatest Recombinante v.3.0 ELISA (Wiener Laboratories, Rosario, Argentina) had higher sensitivity (94.0–97.1%) than the Hemagen Chagas' kit ELISA (Hemagen Diagnostics, Inc., Columbia, Maryland, USA) (88.0–92.0%) while the Hemagen kit had somewhat higher specificity (99.0–100% versus 96.5–99.3%). Samples from donors in South America had the highest levels of antibody reactivity and clinical sensitivity. Those from Central America were intermediate and antibody reactivity and clinical sensitivity was lowest in donors from Mexico.

A comparison of the performance of the four FDA-cleared serological tests with three latest-generation tests has been conducted using blood donor plasma samples [20]. The Abbott PRISM Chagas chemiluminescent assay (Abbott Laboratories, Abbott Park, Illinois, USA) is FDA approved for screening in blood and organ donors but not cleared for diagnostic use. Wiener Lisado and Wiener v.4.0 ELISAs (Wiener Laboratories, Rosario, Argentina) are not FDA cleared for use in the United States. All three tests demonstrated 100% specificity (95% CI, 98.6, 100). Wiener Lisado and Wiener v.4.0 had sensitivities of 97.1% (95% CI, 95.1, 98.4) and 98.9% (95% CI, 97.4, 99.6), suggesting that each could improve diagnostic sensitivity while maintaining high specificity.

The diagnosis of congenital Chagas disease is confirmed by detection of motile trypomastigotes microscopically in fresh anticoagulated blood specimens, by presence of trypomastigotes in Giemsastained blood smears from whole blood or buffy coat or by PCR testing of whole blood [4]. PCR has higher sensitivity than microscopy and is the diagnostic

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test of choice [21]. Histopathologic examination of the placenta can reveal intracellular parasites [22]. PCR is available for diagnosis of congenital *T. cruzi* infection in the United States, through the CDC Parasitic Diseases Reference Laboratory, as well as in Spain and Italy [4,8■■,10].

An IgM trypomastigote excreted-secreted-antigen (TESA)-blot has been developed to detect shed acute phase antigen (SAPA) within the first 3 months of infection [23]. The anticipated use for the assay is in endemic regions where PCR may not be available. It is more sensitive than micromethod examination of infant blood buffy coat but less sensitive than PCR. Cumulative sensitivity of the IgM TESA blot in a study of biorepository samples from Bolivia and Peru was 80% (95% CI, 59–92) and specificity was 94% (95% CI, 92–96) [24]. In a validation cohort from three hospitals in Santa Cruz, Bolivia, a newly developed IgM-SAPA ELISA performed with accuracy similar to PCR in evaluation of 77 congenital cases, indicating its potential for use in regions currently relying on microscopy [25]. Finally, a *T. cruzi* loop-mediated isothermal amplification molecular test kit with the potential for visual reading of fluorescence, developed with the aim of minimizing need for laboratory facilities, shows promise through testing of stored specimens but requires further validation [23,26,27].

PREGNANCY-BASED SCREENING IS COST-EFFECTIVE

Targeted or universal maternal screening with infant testing and maternal and infant treatment for confirmed Chagas disease would be cost saving in the United States [28■]. At current testing costs, maternal screening, infant testing and treatment are cost-saving for maternal prevalence as low as 0.057% and for mother-to-infant transmission probability as low as 0.001%. Targeted screening, including treatment with benznidazole, would result in savings of $1314 per birth and $670 million in lifetime savings per birth-year cohort.

OVERCOMING BARRIERS TO IMPLEMENTATION AND ADHERENCE TO PREGNANCY-BASED SCREENING PROGRAMS

A number of identified barriers exist to instituting and maintaining adherence to pregnancy-based screening programs in nonendemic regions (Table 2). These include the need to improve knowledge of Chagas disease among Latin American women living in these regions and to equip them to request testing [29]. Educational materials, such as the poster in Fig. 1, available from the CDC in English and Spanish, displayed in prenatal clinics, could increase awareness. Healthcare providers in obstetrics and gynecology and family medicine perceive barriers such as unfamiliarity with which patient populations are at risk, and being unsure of how to order *T. cruzi* screening serology and how to act upon a positive test result [30]. Education, directly and by use of electronic medical record prompts, could address these concerns [31]. The issue of cost for testing is potentially a major barrier, but if *T. cruzi* serology is included with testing for such infections as hepatitis B, HIV, rubella and syphilis, it could be bundled into the charge for pregnancy and delivery care.

A successful screening program requires follow through, with referral of mothers identified as *T. cruzi* positive for cardiac evaluation after delivery and treatment after completion of

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breastfeeding, of screening other children and maternal relatives and assuring that infant evaluation, including early PCR testing, is coordinated. Sustainability should also be a goal. In one region in Spain that recommended universal screening for pregnant Latin American women in 2007, a pilot study in 2009–2010 showed very high adherence to a screening protocol (>95%) but by 2014–2018, adherence had declined to 40% [29]. Providing easily accessible learning opportunities, such as online training sessions, is one mechanism that has been effective in raising awareness and educating healthcare providers [31].

CONCLUSION

Congenital transmission is an important source of *T. cruzi* infection in endemic regions and in nonendemic regions where women at risk for Chagas disease reside. Pregnancy is the optimal access point for Chagas disease screening because both mother and infant have contact with the healthcare system at delivery [28■]. Successful implementation of systematic pregnancy-based *T. cruzi* screening in at-risk women living in nonendemic regions, evaluation of infants born to *T. cruzi*-positive women, treatment of mothers and neonates with confirmed infection and screening maternal relatives offers hope that such programs will be widely implemented. Although barriers exist to implementing and sustaining such programs, these could be overcome through education and by adherence to care coordination protocols that will result in identification and cure of congenital infections and reduced morbidity from chronic Chagas disease.

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KEY POINTS

- Congenital Chagas disease is a global concern as the result of migration of mothers with chronic *T. cruzi* infection to nonendemic regions.
- Congenital transmission is an important route of *T. cruzi* infection, now estimated to account for 22.5% of new infections.
- Systematic serologic screening of at-risk pregnant women and evaluation and treatment of infants born to mothers with *T. cruzi* infection should occur in nonendemic regions to optimize outcomes for mothers, infants and family members of index patients.
- PCR is the assay of choice for the diagnosis of congenital Chagas disease.
- Barriers to implementation of pregnancy-based screening for *T. cruzi* could be overcome by education of mothers and healthcare providers and by well structured care coordination efforts.

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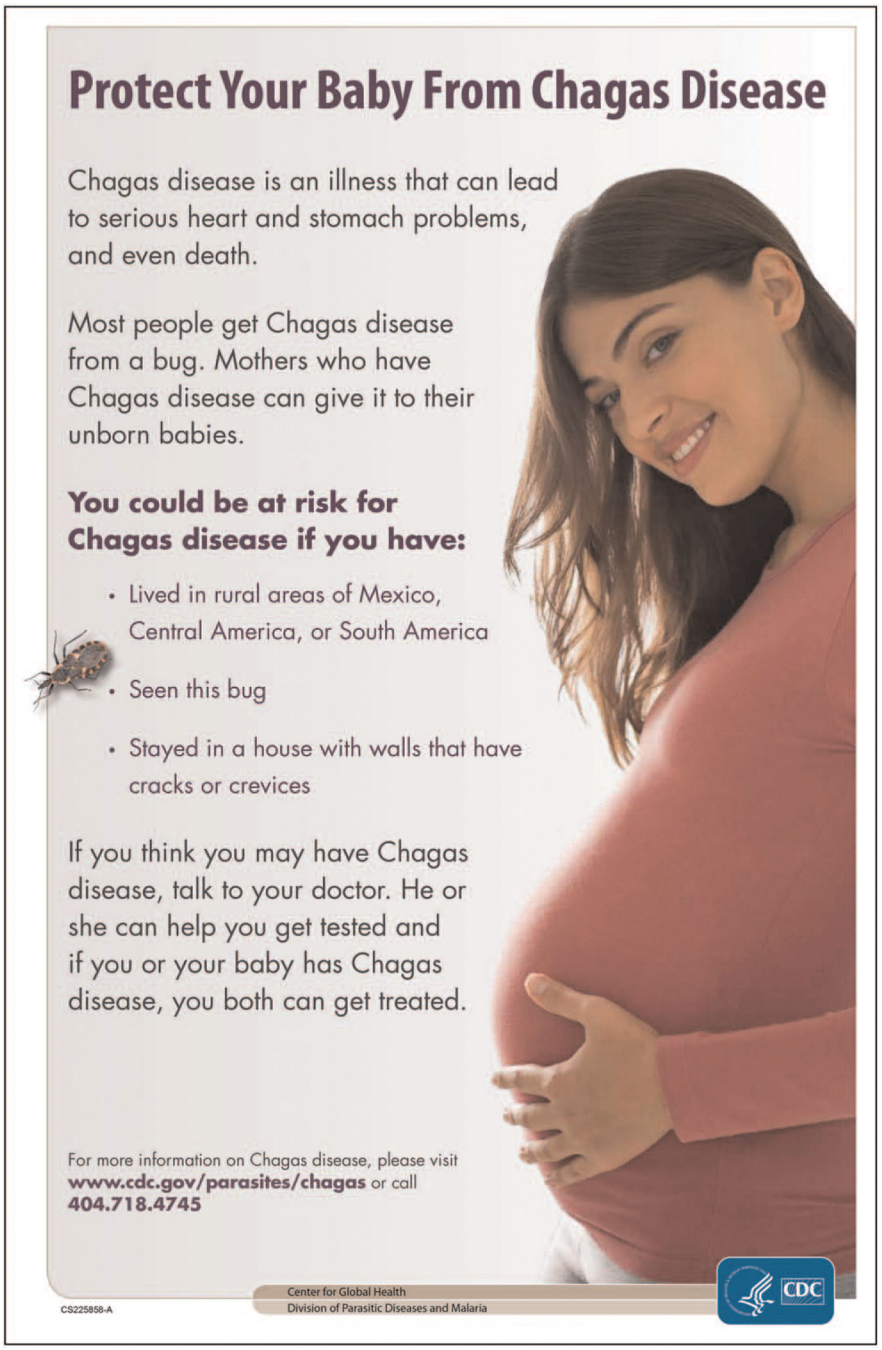

FIGURE 1.

Poster available from the Centers for Disease Control and Prevention to promote maternal screening for at-risk mothers and their infants (https://urldefense.proofpoint.com/v2/url?u=https-3A__www.cdc.gov_parasites_chagas_resources_poster-5Fchagas-5Fprotect-5Fyour-5Fbaby.pdf&d=DwIGaQ&c=ZQs-KZ8oxEw0p81sqgiaRA&r=NadI6Qi57JUPVBuvPZEL_g&m=10mA-

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O2nJGphNcEcp44dfH_vVTeDGqisw74mscpCraE&s=Thh73-8qgroB7J4SsnsNg2Opr1ubq2QF_42GwcApfts&e).

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Table 1.

Components of a comprehensive pregnancy-based screening program for congenital Chagas disease

Maternal
A mechanism is established to identify women at risk for Chagas disease
An initial *Trypanosoma cruzi* IgG screening test is performed during a prenatal visit for all at-risk women and results are entered into the medical record
A second *T. cruzi* IgG test using a different antigen or serologic technique is performed during a prenatal visit for screen-positive women and results are entered into the medical record
Confirmatory testing is performed during a prenatal visit if serologic test results are discrepant
Test results are available at delivery and a mechanism is in place to notify neonatal healthcare providers of the maternal status Mothers confirmed as having Chagas disease are referred for clinical evaluation after delivery and for treatment after completion of breastfeeding
Neonatal
Infants born to women with Chagas disease undergo clinical evaluation for signs of congenital Chagas disease and PCR testing of cord or infant blood for *T. cruzi* during hospitalization
Infants with a positive *T. cruzi* PCR result have repeat testing to exclude contamination with maternal *T. cruzi* DNA
Infants with a negative *T. cruzi* PCR result have repeat testing at 1 month of age since parasite load may increase in the first weeks of life
Infants with confirmed congenital Chagas disease receive treatment with benznidazole
Infants of mothers with chronic *T. cruzi* infection who had negative PCR results and those who did not have PCR testing undergo serologic testing at 9–12 months of age to document or exclude congenital infection
Family members
The mother's other children, maternal siblings and her mother (the infant's grandmother) undergo serologic testing for *T. cruzi* IgG Family members with positive *T. cruzi* IgG are referred for clinical evaluation (to include ECG) and antitrypanosomal treatment

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Table 2.

Overcoming barriers to pregnancy-based screening for congenital Chagas disease

Barrier	Approach to overcoming barrier
Maternal	
At risk mothers' lack of awareness of morbidity of Chagas disease	Increase knowledge; empower women to request testing
Healthcare provider	
Lack of knowledge of Chagas disease	Educational programs; medical record prompts
Time to educate patients	Restructure appointments; add personnel for patient education
Lack of familiarity with ordering screening test	Educational sessions; medical record prompts
Lack of familiarity with obtaining confirmatory test	Educational sessions; medical record prompts
Decision-making for confirmed positive test	Consultation with a Chagas disease expert
Other considerations	
Cost of testing	Bundled into charges for pregnancy-based serologic testing
Adherence to referral of mother after delivery and family member evaluation	Care coordination
Adherence to assessment and treatment of newborns at risk	Care coordination

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