First Colombian consensus on congenital Chagas and clinical approach for women of child-bearing age diagnosed with Chagas

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Abstract

Congenital transmission of Chagas disease has not been extensively studied in Colombia, and there are no standardized processes in the health system regarding the specific diagnosis, treatment and follow-up of this disease. To generate recommendations on congenital Chagas disease and Chagas in women of childbearing age in Colombia, a consensus of experts was developed. An extensive literature search through the Medline database was carried out using the MeSH terms: «Chagas disease/congenital», «prevention and control», «diagnosis», «therapeutics» and «pregnancy». Appropriate abstracts were selected and the full texts were analyzed. The relevant information was synthesized, classified, and organized into tables and figures and was presented to a panel of experts, which was composed of 30 professionals from various fields. Based on the Delphi methodology, three rounds of consultation were conducted. The first and second rounds were based on electronic questionnaires that measured the level of consensus of each question among the participants. The third round was based on a face-to-face discussion focusing on those questions without consensus in the previous consultations. The evidence was adapted to national circumstances on a case-by-case basis, and the content the final document was approved. These recommendations are proposed for use in routine medical practice by health professionals in Colombia.

Primer consenso colombiano sobre Chagas congénito y orientación clínica a mujeres en edad fértil con diagnóstico de Chagas

Resumen

La transmisión congénita de la enfermedad de Chagas ha sido poco estudiada en Colombia y existen pocos procedimientos rutinarios en el sistema de salud para el manejo de esta enfermedad. Por ello se desarrolló un consenso de expertos dirigido a generar recomendaciones de diagnóstico y tratamiento de Chagas congénito y orientación a mujeres en edad fértil. Con ese propósito se realizó una búsqueda extensiva de la literatura, empleando una combinación de términos Mes (Chagas, Chagas congénito, prevención, control, diagnóstico, tratamiento y embarazo) para reflejar el estado del arte en cada tema de interés. Después de ello, se leyeron los resúmenes y aquellos seleccionados para análisis del texto completo. La literatura relevante se sintetizo, clasifico y organizo en tablas y se presentó al panel de expertos, el cual estaba constituido por 30 profesionales en diferentes áreas. Mediante la metodología Delphi se realizaron 2 rondas de cuestionarios virtuales y una reunión presencial en los cuales se evaluaron los niveles de acuerdo entre los participantes. Los puntos con falta de consenso durante las 2 rondas virtuales se expusieron durante las mesas de discusión en la ronda presencial. La evidencia utilizada se adaptó a las particularidades nacionales según el caso y se aprobó el contenido del documento final. Se propone que estas recomendaciones sean usadas por profesionales de la salud en Colombia.

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Introduction

The congenital transmission of Chagas disease poses a challenge in the control of this parasitic disease, since it not only does it affect endemic countries in Latin America but also non-endemic countries in other continents where, because of migration, there are women of childbearing age carriers of *Trypanosoma cruzi*[1] infection.

Comprehensive care for this disease includes not only early detection and treatment of the newborn or infant, but also new challenges in care and medical guidance for infected women. In Colombia, there is little academic production on this matter. For this reason, the country is an adequate scenario to outline a review of the strategies that have shown efficiency in countries and similar contexts and to discuss the suitability of each of these strategies in the national context. Therefore, this first consensus seeks to integrate experts on issues related to pediatrics, prenatal care and health care system stakeholder's, daily decisions makers for this this group of women and children, along with experts in Chagas disease, so as to issue recommendations for the care of these populations in Colombia.

Objective of the consensus

To generate a series of recommendations on diagnosis, follow-up and treatment of congenital Chagas and to guide fertile women with Chagas in Colombia.

Clinical Questions answered in the consensus

- What is the prevalence of *T. cruzi* infection in pregnant women in Colombia?
- What is the risk of congenital transmission of *T.cruzi*?
- What are the most appropriate tests and procedures for diagnosis of *T. cruzi* infection in pregnant women and newborns?
- What are the recommended drugs for the etiological treatment of Chagas' disease in newborns and infants?
- What are the basic recommendations for the etiological treatment of Chagas disease for fertile women with confirmed diagnosis?
- What are the complementary public health measures for the management of congenital Chagas?

Patients to whom the consensus is addressed

Pregnant women in Colombia, newborns and women of childbearing age.

Consensus Users

Medical services, health care institutions, public health groups at municipal, departmental and national level in Colombia.

Methodology

Review of the bibliography and evaluation of the evidence

Literature search related to epidemiology, transmission, diagnosis, treatment and public health strategies for the vertical transmission of *T. cruzi* and congenital Chagas from 1980 to April 2013 was performed. The following Algorithms were designed within the Medline information base: ([«Chagas Disease/congenital»{Mesh}]); («Chagas disease/congenital»[Mesh]) AND «prevention and control»(Subheading); Chagas disease/congenital»[Mesh]) AND«Diagnosis»(Mesh) OR ([«Chagas disease/congenital»{Mesh}] AND «Chagas disease/diagnosis»[Mesh]); («Chagas disease/congenital»[Mesh]) AND «Therapeutics»[Mesh]OR ([«Chagas disease/congenital»{Mesh}] AND «Chagas disease/therapy»[Mesh]) and («Pregnancy»[Mesh]) AND «Chagas disease»[Mesh] NOT ([«Chagas disease/congenital»{Mesh}])

It also included the literature submitted by experts and derived from secondary research from other consensus published on the same subject. The bibliography was selected by summaries, after which the full text of the publication was evaluated. Publications with duplicate information were removed from the record for analysis. When the information of the same article was relevant for more than one topic, it was included in several searches. The data extraction from the articles was done by evidence graphs, verifying the data and the ratios reported and, in some cases, the ratios were calculated from the data provided in the text of the articles. The evaluation of each publication is carried out) through the methodology of reporting of observational studies for the evaluation of the evidence (STrengthening the Reporting of Observational studies in Epidemiology [STROBE]).

Development of expert consensus based on Delphi methodology

The inclusion of experts was based on the recommendations described by McGinis et al.[3] Panels of 3 experts per theme were organized for each of the aspects related to decision making for the identification and management of congenital Chagas disease in the areas of: gynecology, pediatrics, infectology or public health, health promotion entities, as well as representatives of the Ministry of Health and departmental health secretariats. In addition, 2 international experts on the specific subject of congenital Chagas participated in the consensus.

The participation of the consultants was administered in 3 rounds, being the first 2 virtual and the last one, face-to-face. These were carried out from December 2012 to May 2013. The questionnaires were sent by electronic mail with hidden carbon copy and reminders for completion. During all the rounds participants were submitted a text with the best available evidence for each topic, accompanied by questions leading to decision making with the patient. During

the first round, she asked about general aspects related to epidemiology, diagnosis and clinical guidance for children, pregnant women and women of childbearing age with Chagas disease through 15 questions questionnaire. During the second round, the results of the first round were presented and evidence was included for questions in which there was no consensus in the first round; In addition, 10 more specific questions were included. During the third round, in person, consolidated results of the previous rounds were presented, disagreements were resolved based on the points of view of the experts from each area and the final version of the document was approved. Throughout the process participants could suggest adding other studies to the searches (Figure 1)

Consensus data analysis

Since the questionnaires were in some cases based on open-ended questions, the responses were analyzed at a qualitative level and similar response groups were organized over the total to establish the percentage agreement. It was considered as a consensus based on a 60% agreement percentage plus the validation of the responses during the third round. In cases where the agreement was below 60%, a new question was drafted related to the same topic in the following round and, if no consensus was reached, it was recorded as a lack agreement (Graph 1).

Classification of evidence and formulation of recommendations

The level of evidence and the degrees of recommendation were assessed and cataloged per the Strength of Recommendation Taxonomy (SORT).
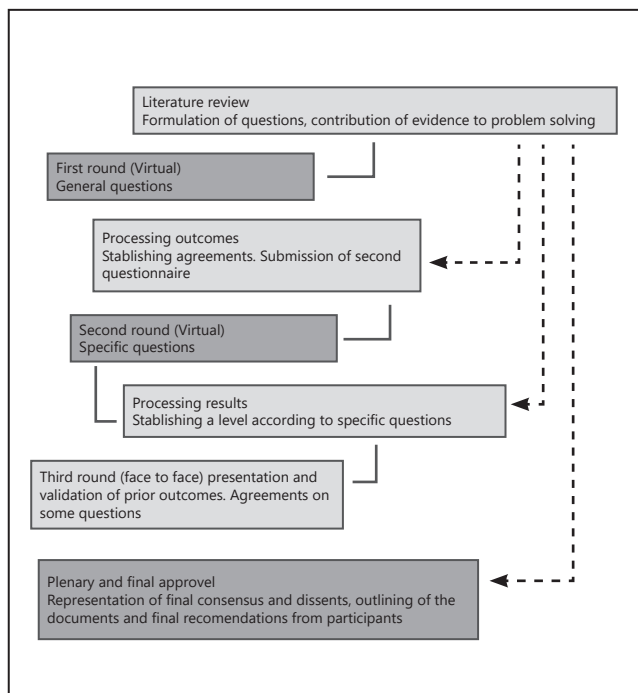
Graph 1. Flowchart for the phases of the consensus

Thus, the quality of evidence was classified into three levels: good, limited, and other. Similarly, the recommendations were classified into 3 categories per the quality of the evidence and the degree of consensus (Graph 2).

Results

In total, 545 titles under the algorithms designed were found, the information provided by the researchers and the review of the gray literature. With the reading of the summaries, 172 texts were chosen for full text reading, of which, finally, 81 texts were included to contribute the evidence presented in the 3 rounds questionnaires. The relevant results of each aspect are shown below:

Section 1. Epidemiology

Prevalence of Chagas in women of childbearing age in Colombia

According to estimates by the Pan American Health Organization, the prevalence of Chagas' disease in Colombia is 437,960 infected and approximately 107,800 women of fertile age (15 to 44 years) suffer from disease[4].There is a lack of precise data on the prevalence of infection in women, both in the general population and in areas where Chagas disease is considered endemic. One of the possible reasons for this lack of knowledge is that screening for diseases such as HIV, toxoplasmosis, syphilis and hepatitis B, but not for Chagas disease, is included during mandatory prenatal care [5,6]. It is estimated that in Colombia there were 665,499 births in 2011[7], and, per estimates of the population at risk of transmission (10.5%), it can be reasoned that about 69,877 of these pregnant women lived in endernic areas.

Table 1. Classification of Degrees of Consensus

Degree of consensus	Percentage of agreement
Perfect consensus	100
Very good consensus	80-99
Good consensus	60-79
Some consensus	50-59

the process was repeated until at least a good level of consensus was reached.

Since there is no information on the prevalence of Chagas disease among pregnant women in the general population, it was decided to consider the prevalence of seropositive individuals in blood bank donors as a reference data to obtain an estimate of the magnitude. However, it is also known that prevalence is usually lower in blood banks[8]. This would be explained by the selection of healthy patients and the repetitive stimulation of the donation by suitable donors[9]. Therefore, considering that estimates of reactivity prevalence for IgG. anti-*T Cruzi* in blood banks vary amongst departments between 0.3 and 0.8% [4,10], it could be gathered that the prevalence in pregnant women is higher than these figures and could be close to 1%.

Graph 2. Classification about the quality of the evidence and level of recommendation contributed by studies, per SORT

Level of Evidence	Diagnosis	Treatment/prevention/screening and prognosis		Level of recommendation	Definition
1	Clinical validated decision Metanalysis/systematic review of high quality studies	Metanalysis, systematic review of RCT studies with consistent findings High quality of individual RCT All or nothing studies	Metanalysis/ systematic review of cohort studies Cohort studies with good follow-up	A	Patient oriented recommendation based on consistent and good quality evidence
2	Non-validated clinical decisions Low quality systematic reviews o studies with non-consistent findings Diagnostic cohort study or case and control diagnostic study	Systematic review/ Metanalysis of low quality clinical studies or studies with inconsistent findings Low quality clinical studies Cohort studies Case and controls study	Systematic reviews or Metanalysis of low quality cohort studies, with non-consistent findings Cohort studies with poor follow-up Case and control study Case series	B	Patient oriented recommendation based on inconsistent or limited quality evidence
3	Consensus guidelines, extrapolations of basic research, common practice, opinions, disease oriented evidence (physiological outcomes) case series for diagnostic studies, treatment, prevention, screening, etc.			C	Recommendations based on consensus, common practice, opinions, disease oriented evidence or case series for diagnostic, treatment, prevention and screening

RCT: Randomized Clinical Trials

Prevalence of Chagas' disease in pregnant women in endemic populations

A recent study determined that the overall prevalence of *T. cruzi* infection in pregnant women from 5 endernic departments was 2.7%, as follows for each department: Casanare: 4.0%; Santander: 3,3%; Boyacá: 3.2%; Arauca: 2.1% and Meta 0.2%, while the range among the 63 participating municipalities oscillated between 0.0 and 20.2%[11]. In addition, a study carried out in 2 municipalities of Boyacá during 2006 and 2007 indicated that the prevalence for Miraflores 4.0% and for Moniquira 2.8%. In conclusion, considering the few local data, it could be estimated that the prevalence of *T. cruzi* infection in pregnant women in endemic Colombian departments ranges from 2% to 4%, while in some municipalities it may reach 20%.

Magnitude of Congenital Chagas Disease

There is confirmed evidence of the congenital transmission of *T.cruzi* in at least 9 cases in Colombia. Six of these were diagnosed by blood culture a study about the endemic area of Boyacá [12,13]; Another 2 cases were diagnosed in the department of Santander; and a case of a premature newborn (28 weeks) in the department of Caldas, who was diagnosed by thick blood smear and 8 days after birth and died due to the infection before receiving treatment. On the other hand, in acute Chagas outbreaks, 2 cases of pregnant women have been reported: one occurred before 20 weeks' pregnancy and led to an abortion and the other in Villanueva Bolivar in a 32 weaker, causing the death of the mother and the child.

In terms of population, the Pan American Health Organization estimates that the annual incidence of congenital Chagas congenital in Colombia is 0.104 and causes an average of 1,000 cases per year[4]. However, there are only two studies in the literature aimed at estimating the magnitude of the problem. The first of one was developed in an endemic area of the department of Boyacá, with a frequency of transmission of 27.3% (6/22) by blood culture, which has been one of the highest frequencies reported in the literature[15]. In contrast, the second study, per preliminary results, has followed done a follow up of 114 children of seropositive mothers in endemic areas from birth and every 3 months up to 12 months of age, and so far, has not shown the presence of cases with the use of parasitological or serological methods[11]. Thus, although in Colombia there is evidence of the frequency of transmission of congenital *T. cruzi,* it is considered that more studies are required and research in grey literature to establish the magnitude of the problem in the country. For now, in the only 2 studies available in Colombia, the frequency of congenital *T. cruzi* transmission ranges from 0 to 27.3%. Graph 3 summarizes the estimates of transmission rates of congenital Chagas based on data from Colombia and other countries.

Cost effectiveness of strategies

Some studies of cost-effectiveness of screening in endemic countries such as Chile, [16] and Bolivia[17], and in non-endemic countries such as Spain[2], indicate a good cost-effectiveness ratio for screening and subsequent follow-up of newborns born to infected mothers and to the women themselves to reduce the burden of disease in both endemic and non-endemic areas compared to not performing the diagnosis. In addition, in other countries, strategies for the active search of cases have been suggested for cases in door to door pregnant women in rural areas difficult to access to improve the coverage of the diagnosis[18]. Preliminary results from a study

in Colombia show that the inclusion of a congenital Chagas' surveillance program is a cost-effective strategy, being more cost-effective in endemic areas[19].

Recommendation 1: Although there is no precise data on the magnitude of Chagas disease in women in pregnant women and newborns in Colombia, estimates suggest that the magnitude is potentially sufficient to consider the inclusion of screening for *T. cruzi* infection in women during pregnancy as part of the test suite during prenatal control. This strategy would potentially be more cost-effective in areas where the disease is considered endemic. Screening is recommended for pregnant women who have lived in recognized endemic areas or have been in contact with risk factors at any point in life. The most widely recognized risk factors are: knowledge of the "pito" vector, ground floor dwelling, palm roof or bahareque wall located less than 2,000 m above sea level, and having relatives diagnosed Chagas. *(perfect Consensus). Level of evidence 3. (Degree of recommendation B).*

Section 2. Diagnosis in pregnant women

As for the diagnostic tests for Chagas' disease in chronic phase, the most appropriate are the serological tests such as the immunoenzymatic test (ELISA) and indirect immunofluorescence (IFI). The reported sensitivity for the ELISA test is 97 to 100%, while its specificity is 96.3 to 100% [20-22]. Regarding the IFI test, it is estimated that it has sensitivity from 93.3 to 100% and specificity from 99 to 100% [21,23]. These results are like those reported in Colombia from both serum and filter paper samples[24]. Furthermore, a recent study in Colombia compared the intra-reproducibility of serological tests for identification of *T. cruzi* infection in pregnant women (ELISA, IFI and indirect hemagglutination-HAI in serum and ELISA on filter paper). This study concluded that the ELISA reproducibility in serum was 0.98, higher than the reproducibility of the other serological tests and well above the ELISA reproducibility on filter paper, which was 0.55[25].

Recommendation 2: ELISA is recommended for serological screening in pregnant women. In a reactive case, confirmation must be made through another conventional serological test with a different principle or with a different antigen, such as IFI or HAI, which has been previously validated in Colombia. (*Good consensus*). Level of evidence 1. (*Level of recommendation A*).

On the other hand, some researchers have evaluated the usefulness of rapid immunochromatographic tests for chronic Chagas' screening with good results in both sensitivity and specificity in the general population, with values above 95% [26-30]. In Colombia, there is only one evaluation report of

Graph 3.

Country	City Región	Years of study	Diagnostic tests on pregnant women	n pregnant women	n positive pregnances	% prevalency pregnant women	Diagnostic tests on babies	n babies	n positive babies	% congenital transmission	Reference
						ELISA, HAI, (6meses)		6	4		
Brasil	Varios estados	1986	HAI, IFI, FC, XD	NA	45	NA	IFI, HAI, ELISA (mayores de un año)	129[d]	4	3,0	[95]
Brasil	Sao Paulo	1998	ELISA, TESA	57	58	NA	MH	54	3	5,5	[96]
Brasil	Pelotas	2004	ELISA, IFI, HAI	351	1	0,3	NA	NA	NA	NA	[97]
Chile	Santiago	1982	NA	NA	NA	NA	MH	482	11	2,7	[60]
Chile	Santiago	2007 y 2008	ELISA, IFI	NA	179	NA	PCR kDNA	179	15	8,4	[98]
Chile		2005 - 2009		4.831	147	3,4	PCR serial (3-18 meses) o ELISA o IIF> 9 meses	127	6	4,7	[99]
Colombia	Moniquirá y Miraflores	2006 - 2007	ELISA, IFI	629	22	3,3	Hemocultivo	22	6	27,3	[15]
España	Murcia	2007 - 2011	ELISA, IFI	NI	59	NI	PCR kDNA	65	9	13,8	[100]
México	Oaxaca	2011	ELISA, Stat-Pack	794	35	4,4	PCR cordón	35	7	20,0	[101]
	Jalisco			557	67	12,0		67	8	11,9	
	México D.F.			97	4	4,1		4	0	0,0	
Paraguay	Asunción	1991 - 1992	ELISA, IFI	840	65	7,7	MH (nacimiento)	28	2	3,0	[55]
				(Asunción)			PCR (nacimiento)		1		
				1.022	107	10,5	PCR, IFI (IgM)	30	3[c]	10,0	
				(San Pedro)							
Perú	Arequipa	NI	NI	3.000	22	0,7	Serología IgM	22	1	4,5	[102]
Perú	Arequipa	2005	ELISA, IFI	3.000	22	0,73	Microhematocrito, IFI y ELISA	22	0	0,0	[103]
USA	Todo el país	1990	NA	2.384.644	61.107	2,6	Estimación	6.360	85-318	1-5 (teórica)	[104]
USA	Todo el país	2000	NA	5.841.538	130.522	2,2	Estimación	12.755	166-638	1-5 (teórica)	
Suiza	Ginebra	2008	IFI	305	6	0,6	IFI, PCR	8	2	25	[105]

ELISA: Enzyme linked immunosorbent assays; FC: complement fixation test; HAI: Indirect Hemagglutination; HC: blood culture; IgM: immunoglobulin M; IIF (IFI) indirect immunofluorescence; MH: microhematocrit; NA: not applicable; NI: no information; PCR polymerase reaction chain; Stat-Pack immunochromatographic rapid test; XD xeno diagnosis. **a:** as there were twins. **b:** historical data from local hospital from 2005-2006

the Stat-Pack test in population from 5 to 18 years of age in the department of Casanare, with a sensitivity of 85.4% and specificity of 98% when compared with conventional serological tests and 46.7% when compared to ELISA on filter paper, showing a lower sensitivity in relation to the studies[31]. A population study of pregnant women from Argentina, Bolivia, Honduras, and Mexico, using umbilical cord blood samples, found that the rapid test on average sensitivity and specificity of 94.6 and 99,0%, respectively, suggesting the use of this test as alternative screening during childbirth[32]. Finally, some studies show that the sensitivity of rapid tests could be affected using whole blood samples, since sensitivity values increase when serum samples are analyzed[33,34]. Although there are limitations are identified in terms of reproducibility, in certain regions, rapid tests could be useful in special situations where there is no alternative, by allowing quick decisions.

Recommendation 3. In cases where the pregnant woman is in labor and there is no previous standard serology for *T. Cruzi* antibodies, an alternative would be the use of rapid test for Chagas on admission to labor. Since the rapid test could have a low sensitivity, in case of a negative result and there are risk factors, the serum test should be administered. A positive test result would lead to the immediate assessment of the newborn, but it will also have to perform confirmatory serological tests on the mother. The use of rapid tests would facilitate the screening strategies; thus, it is necessary to encourage validation studies in the national and especially rural context. *(Good consensus). Level of evidence 2. (Degree of recommendation B).*

Section 3. Diagnosis in the newborn

Microhematocrit in the newborn. This parasitological method of blood concentration from capillaries allows the microscopic identification of *T. cruzi* in movement, by reading the leukocyte phase in the slide, a procedure that includes the rupture of the capillary. Its main advantage is that it can be performed on the first level settings and requires a low volume of blood, which is ideal for newborns[35]. In classical studies, it is estimated that the sensitivity of this test varies between 80 and 90%[36]. Later in Bolivia the so-called *modified microhematocrit* was introduced, which consists on the direct visualization of the capillary without requiring its rupture, generating better biosafety conditions in the procedure and additionally allowing the estimation of the parasitic load. The quantification of the load has allowed to determine a direct relation of the level of parasitemia, detected by modified microhematocrit, with the severity and lethality of congenital Chagas disease. There is a recent modification to this method called "Eppendorf" micro method, which consists of taking the sample in conical plastic vials ("Eppendorf") of 1.5 ml, in place of capillaries. This test has shown excellent operational characteristics compared to xenodiagnostics in Argentina. These 3 concentration techniques (*microhematocrit, modified microhematocrit modified and "Eppendorf" micro method*)

have been widely recommended at international level, as a routine test for the diagnosis of congenital Chagas during the first months of life[39]. These tests can be performed from cord blood or peripheral blood, having a better performance during the first months of the child's life and increasing the possibility of detection with the repetition of the test and with an optimal training of the reader[40]. In Colombia, this method has been used for the diagnosis of acute Chagas in endemic areas and for research of congenital Chagas, in reference centers.

Recommendation 4. It is recommended to carry out concentration parasitological tests (*microhematocrit and modified microhematocrit and "Eppendorf" micro method* for the diagnosis of congenital *T cruzi* infection in the newborn and during the first months of life. (Excellent c*onsensus). Level of evidence 2. (Degree of recommendation B)*.

Recommendation 5. Given that the performance of the concentration tests depend to a large extent on the skill of the operator, it is recommended to train health service personnel so they are administered properly, especially in institutions where deliveries take place. *(Very good consensus). Level of evidence 2. (Degree of recommendation B)*.

Serological tests in infants. It is known that serological tests for the detection of anti-*T cruzi* IgG are useful for the diagnosis of congenital Chagas only after enough time has elapsed that allows the removal of passive IgG antibodies from the mother, so that the detected antibodies do correspond to the the baby[39]. According to different investigations, the time for the removal of maternal IgG antibodies varies. While a study in Santa Fe, Argentina, evidenced the elimination of maternal antibodies to at 6 months,[41] other investigators have proposed a threshold of 8[39,42] or 9 months, [43,44] for the performance of these tests. Finally, there are some proposals to perform the serological tests at month 12 as it coincides with the date of application of vaccines and other public health interventions[45]. Alternatively, the Shed Acute Phase Antigen (SAPA) antigen, expressed mainly in the acute phase of the disease, has been proposed for the diagnosis in infants as of 3 months of age. This is because anti-SAPA IgG class specific antibodies transferred from the mother to the baby transplacentally are eliminated from the baby between days 30 and 90. Different studies performed using SAPA antigen in an ELISA test showed their potential for the diagnosis of congenital infection. A limitation for the use of this test is the low availability of the antigen.

Recommendation 6. It is recommended that in situations where the initial parasitological tests are negative, the determination of congenital infection by means of conventional *T-cruzi* anti- IgG serological tests is administered at 8 months of age. Any negative test at that time discards congenital transmission. Any positive test at 8 months should be confirmed after 10 months by 2 serological tests with different principles. *(Very good consensus). Level of evidence 2. (Degree of recommendation B)*.

PCR: In a Colombian study, the polymerase chain reaction (PCR) displayed a sensitivity of 88.8% and specificity of 92.5% for chronic Chagas' disease in an adult population[50]. In addition, other studies in Colombia have shown 80% sensitivity and 100% specificity in adult patients[51], it is recommended to take serial samples at different times to increase the likelihood of detecting parasites in the sample. However, there are no local studies that allow to have these estimates about the use of this test for diagnosis of congenital Chagas in Colombia. On the other hand, international publications show that

PCR could have a great diagnostic value of the congenital infection and especially the real-time PCR (qPCR) given its: sensitivity higher than that of parasitological tests, early detection of congenital infection, quantitative result (parasite load) and information of epidemiological interest as the determination of lineages of the parasite[53-56.] However, in the latter years it has been reported that *T cruzi* DNA can be transferred transplacentally, being able to circulate for a time in the baby without infection and suggesting that the use of the PCR test is should be after 3 months old to avoid false positives[57]. Despite the potential benefits of the test, it must be considered that it requires a specialized infrastructure and that it is still in the process of standardization and validation in the different laboratories of the endemically countries[68,59]. Therefore, PCR is not recommended as a routine method for diagnosis[33,39].

Recommendation 7. Polymerase chain reaction (PCR) test has shown its potential for the detection of *T. cruzi* congenital infection. However, this test requires more laboratory infrastructure than conventional tests and additionally it needs to be validated specifically for the newborn population. On this basis, it is not recommended to incorporate this test into the routine diagnosis until the above criteria are met. *(Good consensus). Level of Evidence 2. (Degree of recommendation B).*

Section 4. Clinical Manifestations of Congenital Chagas Disease

Between 60 and 90% of cases with congenital Chagas disease may be asymptomatic. Symptoms may appear at an early stage if be it appears during the first 30 days of life, or later, if it appears after this period[36]. There are no pathognomonic symptoms, but some authors have reported that clinically some of the most severe forms of the disease do not differ greatly from infections of the TORCH group (toxoplasmosis, rubella, cytomegalovirus, herpes, and others) Such as low birth weight, prematurity, generalized edema, hepatosplenomegaly, respiratory distress and some more severe cases of hydrops fetalis and death [37,60]. With regards to the association of prematurity with congenital infection evidence is disparate, as some authors have reported a decrease in the gestational age of infected infants compared to healthy infants[61], there are other investigators who do not find any difference regarding the age at birth between the children of infected and non-infected mothers [48]. -hepatomegaly and splenomegaly are among the most commonly

reported signs in congenital cases[48,60,62] and there are also low frequency symptoms, such as anasarca, petechia, myocarditis and meningoencephalitis[60,62,63]. Although the presence of symptoms and signs does not usually reach high percentages, the presence of them should warn the treating physician to the possibility of congenital Chagas[57].

Recommendation 8. It is recommended that newborns with clinical signs such as low birth weight, prematurity, respiratory distress, hepatomegaly, splenomegaly, neurological anomalies, cardiomegaly, hydrops fetalis, fetal death and with an epidemiological history associated with *T. cruzi* infection are discarded the diagnosis of congenital Chagas, using the appropriate technique given the case. *(Excellent consensus). Level of evidence 2. (Degree of recommendation A).*

Section 5. Etiological treatment of newborns

The effectiveness of the etiological treatment in children with congenital infection during the first year of life is considered to be close to 100%, with disappearance of parasitemia and seronegativization after a few months' posttreatment. These findings have been consistently published in studies conducted in Paraguay, Argentina[53'64-66] and Botivia[4o, 42,45] among others. Thus, the goal of etiological treatment in the baby is clearly the cure, as evidenced by all methods.

Recommendation 9. The efficacy of trypanocides treatment for children with congenital Chagas' disease is close to 100% before the first year of life and, therefore, etiological treatment at an early stage is recommended for all cases. The criteria for healing is the negative results in parasitological and serological tests. *(Very good consensus). Level of evidence 1. (Degree of recognition A).*

Per international recommendations and although there are no comparative clinical trials between the two available drugs (benznidazole and nifurtimox), both are used to treat congenital cases[39]. Recommended dosage is specified in Table 4.

Section 6. Etiological treatment of women in child-bearing age

The objectives of etiological treatment are to eliminate infection, reduce parasitic burden and reduce the likelihood of complications and death [67,68]. In observational studies there is evidence of the positive effect of etiological treatment on the elimination or reduction of parasitaemia[69] and there is some evidence of its effect on the reduction of morbidity and mortality in adult patients treated with benznidazole[70-72]. To reach the highest levels of evidence, clinical trials such as: Adult Treatment (TRAENA) in Argentina and the Benznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) clinical trial are being developed in a multi-centered way in 5 endernic countries[74]. On its side, the Colombian guideline for the integral treatment of Chagas disease recommends that etiological treatment should be offered to all patients

Graph 4. Dosing of etiological treatment for children with congenital Chagas

Medication	Dosage	Length of Treatment	Daily dosage	Administration	Presentation
Benznidazole	10mg/kg/day (children < 1 year) 5-7 mg/kg/day (> 1year) 10-15 mg/kg/day	60 days	2 to 3	Oral	12,5, 50 and 100 mg tablets
Nifurtimox	10-15 mg/kg/day	60 days	2 to 3	Oral	120 tablets

under 18 and, per medical criteria, for adults in the chronic phase[6]. Therefore, etiological treatment for fertile women is indicated with different levels of evidence and strength of recommendation, being a population that could benefit for it as they are mainly young and asymptomatic.

Moreover, there is increasing evidence of the benefit of etiological treatment in women for prevention of congenital transmission in future pregnancies[75]. Etiological treatment is clearly contraindicated during pregnancy. During the chronic phase of the disease, it is recommended to postpone the initiation of etiological treatment during nursing, in order not to alter the mother-child bond in the event of adverse effects of the medication on the mother. When prescribed in fertile women, contraception should be provided because trypanocides drugs have teratogenic potential.

Recommendation 10. It is recommended to provide etiological treatment with benznidazole or nifurtimox to fertile women. It is contraindicated during pregnancy and it is recommended to delay the start of treatment until the end of nursing. In all cases, contraception is recommended for fertile women during the administration of etiological treatment for Chagas. *(Very good consensus). Level of Evidence 2. (Degree of recommendation B).*

Adverse effects of etiological treatment

Etiological treatment with available trypanocides (benznidazole or nifurtimox) may generate some adverse effects; However, these drugs are always better tolerated in children than in adults[76]. Adverse effects can be well controlled through appropriate symptomatic management and the possibility of rigorous medical follow-up allows the completion of treatment in more than 85% of patients.

Recommendation 11. It is recommended that the patient be informed in advance about the possibility of adverse effects of the etiological treatment of the Chagas disease. It is also recommended that patients receive constant medical follow-up during the treatment period, to promote good adherence to treatment, as well as the end of treatment. *(Very good consensus). Level of evidence 2. (Degree of recommendation B).*

Section 7. Considerations about activities in the family of the pregnant woman

The recommendation to study the relatives of patients with

congenital Chagas 'disease and pregnant women with Chagas' disease is widely disseminated[39,45,67]. Since congenital infection can occur in one or more children of seropositive pregnant women, it is possible that there are children older than the neonate with an undiagnosed congenital infection[77]. In addition, in a local study in Casanare, Colombia, the prevalence of Chagas disease in relatives of positive pregnant women was 9.8%. Other studies in Argentina have found that being a sibling of a child infected with *T. cruzi* is a risk factor for acquiring the infection, which indicates that family members should be targeted by screening programs[33].

Recommendation 12. Diagnostic activities for the family group of HIV-positive mothers (with emphasis on children) are recommended to confirm other possible cases and ensure access to treatment and follow-up. *(Excellent consensus). (Level of Evidence 1). (Grade of recommendation A).*

Recommendation 13. Comprehensive counseling is recommended at the time of diagnosis to both the pregnant woman and her family, with a clear orientation regarding comprehensive treatment and mental health support to minimize the impact of the diagnosis. *(Excellent consensus). (Level of Evidence 3). (Degree of recommendation C).*

Section 8. Considerations on vector control and other public health measures

Vector control, not only has an impact on the most important transmission route (vectorially), but it is also an indirect control tool for congenital Chagas[79] because it reduces the likelihood of new infected mothers or seropositive mothers who have been reinfected, avoiding parasitemias that make mother-child transmission more likely[80]. Some studies in Bolivia have shown that the children of mothers from areas with higher exposure to reinfection, caused by a higher vector presence, are more likely to have worse outcomes at birth, such as lower birth weight or postpartum complications[81]. Similar findings in Bolivia confirm that there is less severity of congenital disease in the absence of reinfection of the mother during pregnancy.

Recommendation 14. Home visits for vector control is recommended and sustained surveillance activities in areas where of HIV-positive pregnant women and persons undergoing etiological treatment for Chagas disease are at risk Vector transmission live. *(Excellent consensus). Level of evidence 1. (Degree of recommendation A).*

Recommendation 15. Given the logistical difficulties of monitoring the mother-child binomial as well as the family background, it is recommended that vector-borne disease control programs integrate efforts and platforms with strategies already in place, such as sexual and reproductive health, indigenous communities and programs for the care of children. *(Excellent consensus). Level of evidence 3. (Degree of recommendation C).*

The consensus recommendations are summarized in Figure 2.

As indicators of the implementation of these recommendations, the following are proposed:

- % of pregnant women with screening tests for *T. cruzi* infection
- % of pregnant women with confirmatory tests for *T. cruzi* infection
- % of children of HIV-positive mothers with parasitological tests the first month of life
- % of children of seropositive mothers with serological tests between 9 and 12 months
- % of children with confirmed diagnosis receiving etiological treatment

Updating process for the consensus
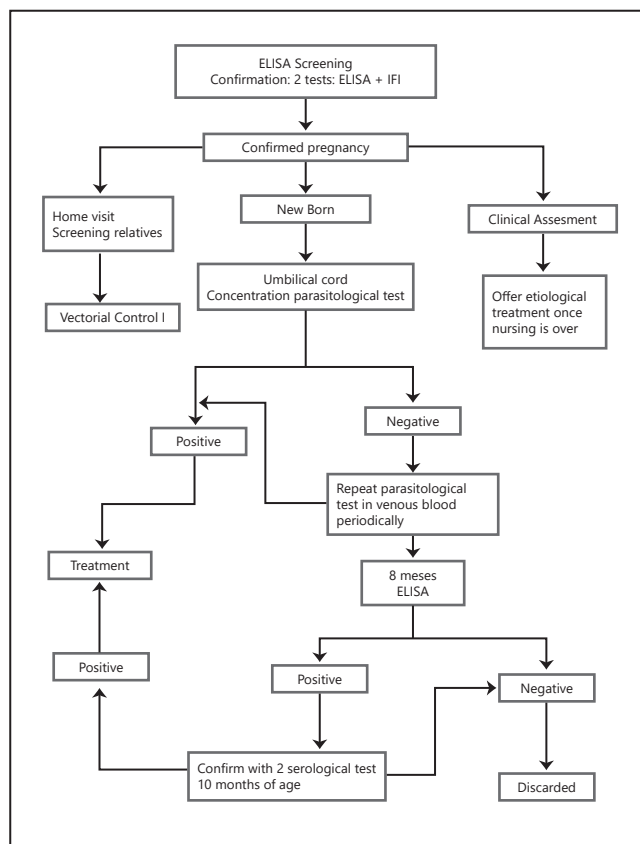
It is suggested to update the consensus every 3 years.

Figure 2: Algorithm recommended by the consensus for diagnostic and treatment of congenital Chagas.

Potential barriers to implementation of recommendations

There are potential barriers, first, the acceptance of the recommendations by health professionals. Second, the dissemination of recommendations in the national territory. Thirdly, the reforms to the health system that eventually modify the roles of the stakeholders or that limit the opportunity of the processes.

Limitations

In Colombia, there is little information about this topic, since most of the evidence presented comes from studies performed in other Latin American countries. Although the consensus was reached with representatives from all sectors of in health care it did not include patients. In addition, the possible limitations due to health reforms generated or implemented after the consensus was drafted, that modify the itinerary of care and responsibilities of the different stakeholder of the system, are not considered.

Conclusion

The methodology for the elaboration of this consensus is based on the compilation and organization of the abundant international experience, in comparison to domestic experience, to establish common points and potential applications to the Colombian context. The recommendations are based on a collective construction from stakeholders from the scientific, clinical and public health care fields of various levels of care related to decision making in this population group. This consensus constitutes the first effort to generate a tool to base the application of practices in the health system that optimize the opportunity of diagnosis and treatment of people infected with *T cruzi*, with emphasis on women and children. Additional efforts on the part of the authorities should be carried out to guarantee the dissemination and application of the recommendations in the national territory. Finally, the consensus update should be given once the evidence on new or better procedures is identified.

Conflicts of interest

It is considered that there is no conflict of interest between the proponents and participants of this consensus.

Acknowledgements

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