Rev. Inst. Med. trop. São Paulo
34 (5): 403-408, setembro-outubro, 1992

POSSIBLE RISK FACTORS FOR VERTICAL TRANSMISSION OF CHAGAS' DISEASE (1)

Achiléa L. BITTENCOURT (2)

SUMMARY

The author emphasizes the importance of the congenital transmission of Chagas' disease and discusses the possible risk factors for transmission such as age, origin, obstetrical history and maternal form of disease. Exacerbation of infection during pregnancy is also considered as a possible risk factor for transmission. Besides, a relationship between the frequency of transmission and gestational age is presented. Concerning breast-feeding, the risk of transmission is directly related to the acute phase of maternal disease and bleeding nipples.

The deleterious effects of chagasic infection on the fetus and newborn are also considered.

KEY WORDS: American trypanosomiasis; Vertical transmission; Congenital Chagas' disease; Breast-feeding.

INTRODUCTION

As the natural and transfusional ways of transmission of Chagas' disease is controlled, the Public Health entities must shift attention to the vertical forms of transmission. The magnitude of this problem and its public health significance have not been sufficiently appreciated until now. In endemic areas of Brazil and of other South-American countries serologic tests for Chagas' disease are not performed during pregnancy.

To emphasize the importance of these forms of transmission it is enough to say that the prevalence of **Trypanosoma cruzi** infection among pregnant women in South America ranges from 2 to 51% in urban centers and from 23 to 81% in endemic areas[14]. The infected mothers even without symptomatology can transmit infection to their offsprings through the placenta and occasionaly through breast-feeding.

In Bahia among non-selected women, there is nearly one case of congenital Chagas' infection per each 1.000 births[10], while in Bolivia the frequency of transmission is much greater, around 7.5%[4].

Transplancentary transmission

We are going to discuss the possible risk factors for congenital transmission of Chagas' disease such as exacerbation of parasitemia during gestation, maternal age, phase of maternal disease, obstetrical history of abortion, prematurity, stillbirths and neonatal deaths, history of a previous case of transmission and, origin of mothers. Also the age of gestation, other associated conditions in mothers and the sex of the concept are considered.

Considering that gestation modifies the immunologic response to infections[16], some studies were done in order to verify if there is exacerbation of parasitemia in Chagas' disease during pregnancy. The results were contradictory. STORNI & BOLSI[34] observed that there is a higher positivity to xenodiagnosis (xenos) in chagasic women during gestation. In contrast, BIOCCA & SEQUEIRA[5] found a higher frequency of

(1) Lecture presented at the meeting "On risk factors for infection and disease in women: Implications for research directions and control measures. WHO, Geneve, May 1989 (actualized).

(2) Professor of Pathology, School of Medicine, Universidade Federal da Bahia, Brazil.
Address for correspondence: Hosp. Professor Edgard Santos, Serviço de Anatomia Patológica, Rua Augusto Viana s/n, Canela, CEP: 40140, Salvador, Bahia, Brazil.

parasitemia in non-pregnant women as compared with a pregnant group. The same contradictory results were observed experimentally[17,25,37]. Recently, MENEZES et al.[30] evaluated the parasitemic profiles of 119 chronically infected women with **T. cruzi** applying xenos during and after pregnancy. They observed that the frequency of positive xenos and the parasitemic levels increased during pregnancy, especially in the third trimester decreasing after delivery. However the differences observed in those two parameters comparing the second and third trimesters were not statistically significant. In that study only 20 mothers had two or more positive xenos during gestation. Among them, the frequency of positive xenos and the level of parasitemia was much higher during pregnancy than after delivery indicating that there is an increase in those parameters during pregnancy. If this ocurrence contributes to aggravate the course of chagasic infection in those mothers, it is a matter for further investigation. One of those mothers who had four positive xenos transmitted the infection transplacentally (unpublished data).

As parasitemia declines with age[23] we could assume that the frequency of transmission would be greater among young mothers. Comparing the mean age of chagasic mothers in general (X: 28,0 ± 6,2 yrs) with the mean age of chagasic mothers who transmitted their infection congenitally (X: 25,52 ± 5,8 yrs), BITTENCOURT[11] found a statistically significant difference.

Congenital transmission of Chagas' disease may occur during any phase of maternal disease. The risk of transmission should be greater in the acute phase when parasitemia is high and persistent. Only eight cases of acute Chagas' disease occurring during pregnancy have been reported and in five of them congenital transmission occurred[14,26]. Among chronic chagasic mothers, the frequency of transmission is around 1.6%[11].

Comparing the frequency of prematurity, abortion, stillbirths and neonatal deaths in chagasic and non chagasic mothers and in a group of chagasic women who transmitted the infection in the last pregnancy, the only significant difference observed was a higher frequency of fetal deaths in the latter group[11]. Perhaps the higher frequency of stillbirths in those mothers is due to transmission of chagasic infection in subsequent pregnancies. Differently from many other congenital infections such as toxoplasmosis and rubella, Chagas' disease can recur in other pregnancies. BITTENCOURT & GOMES[6] observed a patient during four gestations and transmission occurred in two alternate pregnancies. ARTEAGA-FERNANDEZ et al.[2] studying retrospectively the children of 45 chagasic women living outside endemic areas for many years found four congenital cases, three of them from one single mother.

As there are geographical differences in the frequency of congenital transmission of Chagas' disease, the origin of mothers may eventually represent a risk factor.

In studies evaluating all births (including abortions and stillbirths), it was observed that the frequency of transplacental transmission is greater below 34 weeks of gestation, occurring mainly between 22 and 26 weeks (Table 1)[7,9]. Studies in Bolivia revealed a greater frequency of transmission, between 26-37 weeks but in those studies only newborns were evaluated[4].

There is no reference in the literature of associated conditions that could increase the chances of transplacental passage of **T. cruzi** in man. In the past, some authors believed that it was necessary to have an associated factor to facilitate the penetration of the parasite[37,38]. But several clinical and experimental observations indicate that transmission can occur in the absence of any previous lesion of the trophoblast[14].

There are various clinical and experimental studies indicating that the male sex is more susceptible to **T. cruzi** infection[18,20,22,29], but there is no agreement in the literature about this matter[35]. Recently, MOTA[31] published the results of a longitudinal 9-year study in Castro Alves (Bahia) that indicated only small differences by sex in the frequency of E.C.G. abnormalities and in the stan-

Table 1
Incidence of congenital Chagas' disease among non-selected mothers in different periods of gestation.

Nº cases	Fetal weight	Gestational age	Incidence of transmission
164	9-200 g	11 - 18 w	0%
136	201-400 g	19 - 21 w	2.2%
195	401-1000 g	22 - 26 w	3.2%
305	1001-2000 g	27 - 34 w	1.3%
400	≥ 2.500 g	≥ 37 w	0%

dardized mortality rates in Chagas' disease. WIDMER & AZEVEDO[39] evaluating the frequency of cardiac parasitism in 264 autopsies observed a higher frequency of parasitism in males than in females. There are no studies comparing the intensity of lesions in different sexes in congenital Chagas' disease but in a group of 35 infected conceptuses I studied, there was a marked predominance of females (22 F/13 M). AZOUGUE & URIOSTE[3] in Bolivia observed only a slight female preponderance (18 F/15 M) among their congenital cases but this preponderance was not observed by other authors[24].

Why transmission occurs in only a small proportion of chagasic mothers is not yet well understood. As observed in relation to clinical manifestations and therapeutical responses, certainly the frequency of congenital transmission is also strain related. Undoubtedly there are geographical differences in the incidence of congenital transmission[14]. Experimentally it was observed a marked difference in the placental tropism of three different strains of **T. cruzi**[1]. The immunologic competence of the placenta may also play an important role in protection. DELGADO & SANTOS BUCH[19] verified in mice that transmission was dependent on pathogenicity of strain and on placental phagocytic capacity. Certainly the placenta protects the fetus against **T. cruzi** infection. Besides macrophages (Hofbauer cells), the trophoblastic epithelium also has phagocytic properties. Parasitism of this epithelium was observed in three placentas and in all of them the concept was free of infection[10]. We have also observed parasites within the chorion of villi in the absence of fetal infection[12].

Until now, we don't know which chagasic mothers will transmit their infection transplacentally. However we could assume that there is a greater risk in younger mothers, during the acute phase of disease, and when the patient presents an exacerbation of parasitemia. Also, mothers with history of fetal losses, previous infected offspring, or living in an area of frequent congenital transmission carry a greater risk.

Reactivation of infection cannot be evaluated only through xeno. There are in the literature few attempts to detect reactivation of **T. cruzi** infection during gestation through serologic tests[33,34,36]. STORNI & BOLSI[34] and SZARFMAN et al.[36] found anti-**T. cruzi** IgM antibodies in the serum of some pregnant chronic chagasic women. As those antibodies are present only in the acute phase of infection, those authors believed that this finding represents an reactivation of infection. Unfortunatelly, STORNI & BOLSI[34] did not correlate their findings with the outcome of the pregnancies. However, among the six pregnant women with specific IgM antibodies described by SZARFMAN et al.[36], two cases of congenital transmission of **T. cruzi** were observed. More recently, REYES et al.[33], detected through ELISA, IgM specific antibodies in the serum of 10 mothers who transmitted their infection to the offsprings but no IgM antibodies were found in the other 12 infected mothers who did not transmit the disease. More studies will be necessary to find a method that could evaluate mothers with a greater risk for transmission.

Considering that there are geographical differences in relation to congenital transmission of Chagas' disease, we believe that it is necessary to make evaluations of the possible risk factors in different endemic areas in South America.

Significance of placental transmission

Besides abortion, prematurity, stillbirths and neonatal deaths, congenital Chagas' disease can also cause infra-uterine growth retardation and deformations[14]. The most common pathological findings are meningoencephalitis, myocarditis, myositis and inflammation of the digestive tract and skin. An important aspect of congenital Chagas' disease is the presence of pneumonitis associated with parasitism of the alveolar wall and the amnionic epithelium. The parasitized amnionic fluid may be a vehicle of accidental transmission of Chagas' disease to professionals involved in obstetrical care[14]. Two important aspects not observed in the non-congenital acute infection are the digestive manifestations and neurologic sequelae. It is important to emphasize that digestive manifestations sometimes with megaesophagus and megacolon may occur very early in congenital Chagas' disease, frequently being present at birth[10]. Congenital chagasic meningoencephalitis may cause different grades of neurologic sequelae and even cerebral palsy and microcephaly. Ocular involvement, such as chorioretinitis and opacification of the vitreous body, have also been reported[14,15]. These observations demonstrate that congenital Chagas' disease can cause deformations quite similar to toxoplasmosis and other congenital infections. The infected newborns may, however, be asymptomatic and remain without clinical manifestations of disease[14,15].

It has been observed that the severity of congenital chagasic infection varies in different geographical areas. It is greater in Bahia than in Cordoba (Argentina) where the congenital cases are generally asymptomatic[32].

Breast-feeding transmission

Breast-feeding is a possible route of Chagas' disease transmission. MAZZA et al.[26] and MEDINA-LOPES[27] found trypomastigotes in the milk of mothers during the acute phase of disease. Until now, there is no proof of milk infection during the chronic phase of disease. MEDINA-LOPES[27,28] reported two infants with acute Chagas' disease acquired through breast-feeding. Both mothers were in the chronic phase of disease. In one of those cases, the search for parasites in the milk was negative and the mother presented bleeding nipples thus infected blood could have been the source of infection.

An evaluation of Chagas' disease transmission through breast-feeding was recently done in 78 chronic chagasic mothers through parasitological study of milk or colostrum and through serological evaluation of 93 lactating children[13]. In this study all the mothers were recommended to avoid breast-feeding in the presence of nipple bleeding. The parasitological study of all mice inoculated with the samples of milk or colostrum and the serological tests performed in the children were negative.

Experimentally it was demonstrated that even in the acute phase of **T. cruzi** infection transmission through breast-feeding rarely occurs unless parasites have been frequently found in the milk. Also, resistence to infection in suckling animals has been observed.

Taking in acount those observations prohibition of breast-feeding for chronic chagasic mothers can not be recommended. However, breast-feeding should be avoided when nipple bleeding occurs. Besides, chagasic mothers should not be accepted as donors in milk bank programs.

The data here presented demonstrate the importance of identifying chagasic mothers in the pre-natal care units. All pregnant women who have lived in rural endemic areas as well as those who have received blood transfusion must be submitted to serological screening.

RESUMO

Possíveis fatores de risco na transmissão vertical da doença de Chagas

A autora enfatiza a importância da transmissão congênita da doença de Chagas e analisa os possíveis fatores de risco tais como idade, procedência, história obstétrica e forma da doença materna. Considera a exacerbação da infecção na gestação como possível fator de risco e relaciona a freqüência de transmissão com a idade gestacional. Os riscos na transmissão pela amamentação são relacionados diretamente com a fase aguda da doença materna e, na fase crônica com o sangramento mamilar. São também abordados os efeitos lesivos da infeção chagásica ao concepto.

ACKNOWLEDGMENTS

We are indebted to Prof. Eduardo Mota for the critical reading, to Dr. Davis Ashford for the English revision and to Miss Irani Abreu for the secretarial assistance.

REFERENCES

1. ANDRADE, S.G. - The influence of the strain of **Trypanosoma cruzi** in placental infections in mice. **Trans. roy. Soc. trop. Med. Hyg., 76:** 123-128, 1982.

2. ARTEAGA-FERNANDEZ, E.; BARRETO, A.C.P.; IANNI, B.M.; VIANNA, C.B.; MADY, C.; BELLOTTI, G. & PILEGGI, F. - Incidência da transmissão congênita na doença de Chagas. **Arq. bras. Cardiol., 49:** 47-49, 1987.

3. AZOUGUE, E. & URIOSTE, G. - Transmission congenita de la enfermedad de Chagas. III. Aspectos clínicos y anatomo-patológicos del recien-nacido. **Bol. Cient. CENETROP, 11:** 21-30, 1985.

4. AZOUGUE, E.; LA FUENTE, C. & DARRAS, C. - Congenital Chagas' disease in Bolivia: epidemiological aspects and pathological findings. **Trans. roy. Soc. trop. Med. Hyg., 79:** 176-180, 1985.

5. BIOCCA, A. & SEQUEIRA, H. - Prevalência de infección chagasica en embarazadas. In: CONGRESO ARGENTINO DE PARASITOLOGIA, 1, Buenos Aires, 1972. **Anales.** p. 43.

6. BITTENCOURT, A.L. & GOMES, M.C. - Gestações sucessivas de uma paciente chagásica com ocorrência de casos de transmissão congênita da doença. **Gaz. méd. Bahia, 67:** 166-172, 1967.

7. BITTENCOURT, A.L. & BARBOSA, H.S. - Incidência da transmissão congênita da doença de Chagas em abortos. **Rev. Inst. Med. trop. S. Paulo, 14:** 257-259, 1972.

8. BITTENCOURT, A.L.; BARBOSA, H.S.; SANTOS, I. & SODRÉ, A. - Incidência da transmissão congênita da doença de Chagas em partos prematuros na Maternidade Tsylla Balbino. **Rev. Inst. Med. trop. S. Paulo, 14:** 131-134, 1972.

9. BITTENCOURT, A.L.; BARBOSA, H.S.; SANTOS, I. & RAMOS, M.E.A. - Incidência de transmissão congênita da doença de Chagas em partos a termo. **Rev. Inst. Med. trop. S. Paulo, 16:** 197-199, 1974.

10. BITTENCOURT, A.L. - Actual aspects and epidemiological significance of congenital transmission of Chagas' disease. **Mem. Inst. Oswaldo Cruz, 79** (suppl.): 133-137, 1984.

11. BITTENCOURT, A.L. - Doença de Chagas congênita na Bahia. **Rev. baiana Saúde publ., 11:** 159-209, 1984.

12. BITTENCOURT, A.L.; MOTA, E.; BARBOSA JUNIOR, A.A. & FERREIRA, M.R. - Placentite hematogênica em mães chagásicas. **Rev. Soc. bras. Med. trop., 19:** 239-242, 1986.

13. BITTENCOURT, A.L.; SADIGURSKY, M.; SILVA, A.; MENEZES, C.A.S.; MARIANETTI, M.M.M.; GUERRA, S.C. & SHERLOCK, I. - Evaluation of Chagas' disease transmission through breast-feeding. **Mem. Inst. Oswaldo Cruz, 83:** 37-39, 1988.

14. BITTENCOURT, A.L. - American trypanosomiasis (Chagas' disease). In: MACLEOD, C. **Parasitic infection in pregnancy and the newborn.** Oxford, Oxford Med. Publ., 1988. p. 62-86.

15. BITTENCOURT, A.L.; MEDINA-LOPES, M.D. & CAMARGO, M.E. - Doença de Chagas. In: DINIZ, E.M.A. & VAZ, F.A.C. **Infecções congênitas e perinatais.** São Paulo, Atheneu, 1991. p. 73-89.

16. BRABIN, B.J. - Epidemiology of infection in pregnancy. **Rev. Infect. Dis., 7:** 579-603, 1985.

17. CARLIER, Y.; RIVERA, M.T.; TRUYENS, C.; PUISSANT, F. & MILAIRE, J. - Interactions between chronic murine **Trypanosoma cruzi** infection and pregnancy fetal growth retardation. **Amer. J. trop. Med. Hyg., 37:** 534-540, 1987.

18. CHAPMAN, W.L.; HANSONS, W.L. & WAITS, V.B. - The influence of gonadectomy of host on parasitemia and mortality of mice infected with **Trypanosoma cruzi. J. Parasit., 61:** 213-216, 1975.

19. DELGADO, M.A. & SANTOS BUCH, C.A. - Transplacental transmission and fetal parasitism of **Trypanosoma cruzi** in outbred white Swiss mice. **Amer. J. trop. Med. Hyg., 27:** 1108-1115, 1978.

20. DVORAK, J.A. & POSTAN, M.L. - Estudios sobre la infección de ratones endogamicos con clones de **Trypanosoma cruzi. Bol. Ofic. sanit. panamer., 103:** 93-105, 1987.

21. GOBLE, F.C. - Lack of effect of sex hormones on the course of experimental Chagas' disease in mice. **J. Parasit., 38** (suppl.): 15, 1952.

22. HAUSCHKA, T.S. - Sex of host as a factor in Chagas' disease. **J. Parasit., 33:** 399-404, 1947.

23. HOFF, R.; MOTT, K.E.; SILVA, J.E.F.; MENEZES, V.; HOFF, J.N.; BARRET, T.V. & SHERLOCK, I. - Prevalence of parasitemia and seroreactivity to **Trypanosoma cruzi** in a rural population of northeast Brazil. **Amer. J. trop. Med. Hyg., 28:** 461-466, 1979.

24. HOWARD, J.E. - **La enfermedad de Chagas congenita.** Santiago, 1962. (Thesis para catedra - Universidad de Chile). 55p.

25. KRAMPITZ, H.E. & DISKO, R. - Retardation of parasitemia, prolongation of life or survival of lactating mice in infections with **Trypanosoma cruzi. Nature** (Lond.), **209:** 526, 1966.

26. MAZZA, S.; MONTANA, A.; BENITEZ, C. & JANZI, E.Z. - Transmission del **Schizotripanum cruzi** al niño por leche de la madre con enfermedad de Chagas. **Mis. Est. Patol. Reg.,** Argentina, **28:** 41-46, 1936.

27. MEDINA-LOPES, M.D. - **Transmissão materno-infantil da doença de Chagas.** Brasilia, 1983. (Dissertação de mestrado - Universidade de Brasilia) 137 p.

28. MEDINA-LOPES, M.D. - Transmissão do **Trypanosoma cruzi** em um caso durante o aleitamento, em área não endêmica. **Rev. Soc. bras. Med. trop., 21:** 151-153, 1988.

29. MENEZES, H. - The importance of sex on parasitemia and on the mortality of albino mice experimentally infected with **T. cruzi. Trop. Dis. Bull., 64:** 357, 1967.

30. MENEZES, C.A.S.; BITTENCOURT, A.L.; MOTA, E.L.A.; SHERLOCK, I. & FERREIRA, J. - Avaliação da parasitemia durante e após a gestação em chagásicas crônicas. **Rev. Soc. bras. Med. trop., 25,** 1992 (aceito para publicação).

31. MOTA, E.L.A. - **Mortalidade em uma população de área rural endêmica para a doença de Chagas. Um estudo longitudinal de nove anos em Castro Alves, Bahia.** Salvador, 1988. (Dissertação de mestrado - Universidade Federal da Bahia). 173 p.

32. MOYA, P.R.; VILLAGRA, L. & RISCO, J. - Enfermedad de Chagas congênita: hallazgos anatomopatológicos en placenta y cordon umbilical. **Rev. Fac. Cienc. méd. Univ. Córdoba, 37:** 21-27, 1979.

33. REYES, M.B.; LORCA M.; MUNOZ, P. & FRASH, A.C.C. - Fetal IgG specificities against **Trypanosoma cruzi** antigens in infected newborns. **Proc. nat. Acad. Sci.** (Wash.), **87:** 2846-2850, 1990.

34. STORNI, P. & BOLSI, F.L. - Embarazo y parasitismo por **Trypanosoma cruzi. Medicina** (B. Aires), **39:** 193-197, 1979.

35. STREBER, F. - Influencia del sexo en infecciones experimentales por **Schizotrypanum cruzi**, Chagas 1909. **Rev. Palud. Med. trop.** (Méx.), **2:** 73-78, 1950.

36. SZARFMAN, A.; URMAN, J. & OTALORA, A. - Specific agglutinin and immunoglobulin levels in congenital Chagas' disease. **Medicina** (B. Aires), **35:** 245-250, 1975.

37. WERNER, H. & KUNERT, H. - Ueber die Ursache von kongenitalen Protozoen Infektionen. **Z. Tropenmed. Parasit., 9:** 17-27, 1958.

38. WERNER, H. & EGGER, I. - Kongenitale Chagas - Einfluss einer **Trypanosoma cruzi** Infektion auf die Embryonalen Wicklung bei trachtigen Mausen. **Z. Tropenmed. Parasit., 22:** 224-234, 1971.

39. WIDMER, C.G. & AZEVEDO, E.S. - Sexo do hospedeiro humano e o desenvolvimento de formas parasitárias do **Trypanosoma cruzi** no miocárdio. **Rev. Inst. Med. trop. S. Paulo, 14:** 109-113, 1972.

Recebido para publicação em 10/02/1992
Aceito para publicação em 02/07/1992