THE EPIDEMIOLOGICAL SIGNIFICANCE OF CHAGAS' DISEASE IN WOMEN

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Little is known about the risks associated with Trypanosoma cruzi infection in non-pregnant and pregnant women. From a limited number of studies it appears that in rural areas, parasite rates and rates of serological positivity are similar in both sexes. Abnormal ECG tracings are consistently more frequent in men suggesting that immunity to T. cruzi may be different in females. Complications arising from Chagas' disease in pregnancy are only infrequently reported. Evidence for increased risk of abortion or prematurity is inconclusive except in cases of congenital infection. Most cases of congenital Chagas' disease have been reported from non-endemic areas and there is a suggestion that parasitemic episodes during pregnancy may influence pregnancy outcome. Preliminary evidence indicates that chronic infection can result in in-utero sensitization via passively acquired maternal antibodies. The review concludes that maternal T. cruzi infection carries risks for the child and these warrant systematic research because of their public health significance.

Key words: Trypanosoma cruzi – Chagas' disease – sex differences – women – pregnancy – sensitization – congenital infection

The epidemiology of any infection reflects the interactions of exposure and host immunity in relation to age – and perhaps, also to gender. Patterns of parasitic infection and disease in females are rarely considered separately from those in males, even though the potential consequences in women may be more serious if infection has an adverse effect on maternal health or outcome of pregnancy. The triatomine vectors of Chagas' disease colonise dwellings and live in close contact with the human population so that exposure, in endemic areas, may be intense from an early age in both males and females. In spite of early exposure, only a relatively small proportion of infected people go on to develop chronic disease. Hudson & Hindmarsh (1985) consider that a biphasic progression of disease is observed in many patients who eventually develop chronic Chagas' disease. Progression from one stage to the other may be different in males and females. Indeed, cardiac pathology and associated mortality are reported to be lower in women despite the fact that pregnancy could trigger an alteration in cell-mediated immunity to Trypanosoma cruzi and exacerbate cardiac disease – as might other factors such as age, nutritional status or incidental disease (Kretzli, 1977; Hoff & Boyer, 1985).

This paper does not deal with the immunology of Chagas' disease but looks at available epidemiological and clinical studies relating to infection in non-pregnant and pregnant women, and on pregnancy outcome. The primary literature on Chagas' disease epidemiology is weak, especially in relation to pregnancy and pregnancy outcome. Nonetheless, it is considered important that the potential long-term effects of infection and disease in women should be highlighted, because interventions which reduce infection in women are also likely to have an effect on children born to them.

PATTERNS OF INFECTION AND MANIFESTATION OF DISEASE BY SEX

Infection – Comparing the prevalence of parasitemia in males and females in field studies is difficult because xenodiagnosis and/or culture techniques are required to detect parasitemias which are only readily observed in the acute phase. T. cruzi infection of many years duration is a low-load parasitosis which produces a nearly consistent low level of parasitemia (Santos-Buch & Acosta, 1985). As

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a result, there are very few field studies in which prevalence of parasitemia has been defined. Hoff et al. (1979) were able to detect 23/116 patients with *T. cruzi* parasitemia in a cross sectional survey in Castro Alves, Brazil, and they found no apparent differences between males and females.

Age-specific serological reactivity was similar in both sexes in Castro Alves, Brazil (Mott et al., 1976), and in Belen, Venezuela (Puigbo et al., 1966) although in Brazil, females over age 10 years had higher geometric mean titres than males.

Given that exposure to infected triatomine bugs is unlikely to differ by sex, it is not surprising that infection rates appear to be similar in males and females.

**Clinical disease** — It is estimated that only about 20% of asymptomatic patients with no significant pathological changes are at risk of developing extensive clinical tissue injury later, and only about 30% of hearts studied at autopsy show evidence of myofiber parasitism. It is considered that pathologic changes produced by *T. cruzi* infection may be the result of the size and frequency of the inocula, genetic susceptibility of the host, tissue tropism or rate of proliferation of the infecting strain or, most particularly, the degree of immunological response the infection may evoke (Santos-Buch & Acosta, 1985).

A number of studies show that certain lesions associated with chronic heart disease occur less frequently in women. Oliveira et al. (1981) found the male/female ratio of apical aneurysm in necropsy reports to be 739:339. Although apical aneurysm is not itself a cause of death, its presence is significantly linked with cardiac death and is a sign of a poor prognosis. In a study by Widmer & Azevedo (1972) there was a significant difference in the frequency with which leiomyomal parasites were found in the heart muscles of female patients. The mean age at death was similar for male and female patients and no obvious selection bias could be identified. The authors suggested that certain host enzymes necessary for parasite development might be sex-linked.

In longitudinal studies in Castro Alves, Brazil, abnormal electrocardiogram (ECG) tracings were significantly more frequent in seropositive men than women despite similar age-specific rates of seroreactivity (Maguire et al., 1983). When the same population was followed up after nine years to assess the development of ECG abnormalities in seronegative and seropositive individuals, it was found that seropositives developed abnormal ECGs twice as frequently as seronegatives (Mota et al., 1990). While there was little difference between seronegative males and females in the rate of development of an ECG alteration, amongst seropositives, the rate for males was 32.3/1000 person years (PYs) compared to 21.1/1000 PYs for females. Ventricular conduction defects developed more frequently in seropositive males (11.2/1000 PYs) than in seropositive females (9/1000 PYs) as did frequent or multiform ventricular extrasystoles (4.8 vs 2.4/1000 PYs, respectively). There was no difference in age-adjusted mortality rates by sex and seropositivity, but in seropositive individuals with an initial abnormal or borderline ECG, the mortality rate at age 40-59 was 20.4/1000 PYs in males compared to 11.2/1000 PYs in females. Other, non-controlled studies, have indicated differential mortality by sex, in favour of females (Forichon, 1975; Pereira, 1984).

In Goiânia, central Brazil, a population-based case-control study amongst unskilled workers also found that the risk of ECG alterations of any kind was greater in males, as was the risk of left anterior hemiblock (Zicker et al., 1990). These associations were stronger amongst seropositive than amongst seronegative subjects.

The consistent pattern seen in these studies with regard to heart disease is not observed for the megasymphondes. A radiological study in a selected hospital population (Rezende, 1975) and a community study in N. E. Brazil (Mota et al., 1984) found the disease more frequently in males but the differences were not significant.

In summary, there is good evidence that females show less evidence of heart disease, suggesting a difference in immunological response by sex. There are, however, geographical differences in relation to the age of onset of clinical disease which indicate that other factors also affect disease rates.

**MATERNAL HEALTH AND INFECTION DURING PREGNANCY**

*Clinical status associated with pregnancy* — Acute maternal infections are rare in preg-
nancy since, in most endemic areas, the acute stage occurs in childhood and is frequently asymptomatic (Teixeira et al., 1978). Only eight acute cases have been reported in pregnancy. All of the women recovered but in five cases, congenital transmission occurred (Bittencourt, personal communication).

It appears that women in the indeterminate and chronic stages of infection have uneventful pregnancies (Bittencourt, 1988). In a study comparing fetal-maternal morbidity in seropositive and seronegative mothers living within a 35 km radius of an urban hospital in Cordoba, Argentina, the only pregnancy complications observed which were significantly higher in seropositive women were polyhydramnios and varicose veins (Hernandez-Matheson et al., 1983).

Parasitic episodes during pregnancy – Pregnancy-associated recrudescence of parasitemia has yet to be definitively demonstrated. Szarfman et al. (1975a) reported increased levels of T. cruzi specific IgM in chronically infected mothers, although this antibody is usually found only in the acute phase of the disease. Using xenodiagnosis, efforts to determine the incidence of parasitemia during pregnancy have yielded contradictory results (Biocca & Sequeira, 1972; Storni & Bolsi, 1979). Bittencourt et al. (1988) screened 71 chronic chagasic pregnant women on whom a variable number of xenos were performed. In this study the same patients were used as a control group after delivery and no significant differences were observed between pregnant and postnatal women. The authors nonetheless concluded that there was considerable risk of parasitemia occurring during pregnancy as 38/77 (49.3%) mothers screened had parasitemia on at least one occasion. Ten (11%) had three or more positive xenos during gestation and one of these mothers had a congenitally infected baby. It was suggested that the more frequent and persistent the parasitemia, the more probable was congenital infection.

In a recent study of ten congenitally infected babies and their mothers – all of whom were in the chronic stage – sera from all the mothers whose offspring were infected were found to have IgM antibodies as detected by ELISA, in contrast to none of the mothers delivering healthy children (Reyes et al., 1990). In these tests, soluble extracts from cultured epimastigotes of T. cruzi were used as anti-
gens, but when recombinant T. cruzi antigens were used, only two mothers were positive for IgM antibodies. These findings were difficult to explain but emphasize the importance of individual antigens for antibody detection.

MATERNAL INFECTION AND OUTCOME OF PREGNANCY

Abortion, stillbirth and low birthweight – Some authors have considered Chagas’ disease to be a cause of second trimester abortion (Castilho & Da Silva, 1976) but Bittencourt (1984) found no difference in the abortion rate of chagasic and non-chagasic women. Maternal Chagas’ disease may increase the risk of prematurity but the distinction between prematurity and fetal growth retardation is not always clearly made (Castilho & Da Silva, 1976). Bittencourt (1984) has reported no increase in pre-term delivery (less than 37 weeks gestation) in chagasic mothers unless the infant was congenitally infected. Abortions and stillbirths are frequently reported in cases of congenital infections and several studies have shown congenital infection to occur more frequently in fetuses weighing <2000 gm (Howard & Rubio, 1968; Bittencourt et al., 1972; Azogue et al., 1985). A higher frequency of stillbirths was also observed in women with a previous history of congenital transmission (Bittencourt, 1984).

Most congenitally infected cases present with low birthweight, and some of these are small-for-dates (Stagno & Hurtado, 1971; Vieira et al., 1983). In experimental work in mice with chronic T. cruzi infection, intra-uterine growth retardation has been observed in the absence of congenital infection (Carlier et al., 1987). The cause of fetal growth retardation was unclear since placental modification was not indicated. Controlled studies on the frequency of low birthweight in otherwise healthy children born to seropositive and seronegative women living in endemic areas would be needed to confirm this association.

Congenital infection – Risk factors for congenital infection are still poorly understood. For a proportion of women, infection of the placenta will occur in the absence of congenital infection (Bittencourt, 1984). Cases of congenital infection have been reported largely in offspring of women who have not lived in an endemic area for a number of years (Howard & Rubio, 1968; Hoff et al., 1978; Azogue et
cases have been reported and it is believed that in these cases the child was infected late in pregnancy and mounted an active immune response. The asymptomatic form of the congenital disease is especially prevalent in Argentina (Moya, 1977) but may not be readily detected at birth. The diagnosis of congenital infection by ELISA detection of IgM antibody may yield false negative results. In a recent study (Reyes et al., 1990) only 50-60% of congenital cases were detected by ELISA. The use of recombinant antigens to detect specific IgM and new IgG specificities raised the detection level to 90%. The new IgG specificities observed most frequently were against a shed acute phase antigen (SAPA), generated during the acute phase of infection in the fetuses but not in their chronically infected mothers.

There is very little information on the frequency with which congenital Chagas’ occurs in endemic areas. In the Moro-Moro population of Bolivia, a 63% seropositivity rate was recorded in children less than one year of age and this led the authors to conclude that congenital transmission occurred frequently in this population (WHO, 1983). The age distribution of the 11 children less than one year was not given but in children less than six months of age it is likely that seropositivity reflected the transmission of maternal antibodies (Miles et al., 1975; Breniere et al., 1983; Moya et al., 1989). Micro concentration techniques alone were used for detection of parasitemia which may account for the apparent absence of circulating parasites in older children. Arteaga-Fernandez et al. (1989) suggested that congenital transmission should be most frequently observed in endemic areas where a much higher proportion of mothers are exposed to infection. Serological studies in Castro Alves have failed to detect infections in children under one year of age (Mott et al., 1976) but investigations in other endemic areas are needed for comparison since both the risk and severity of congenital infection are known to vary by region.

Bittencourt found the highest proportion of congenital cases between 19 and 26 weeks gestation in conceptuses weighing <1,000 gms (1988). In Bolivia the largest number of congenital cases was found in newborns weighing between 1,000 and 2,500 gms with a gestational age between six and eight months (26-37 weeks) (Azogue et al., 1985). No positive cases were found before the sixth month of gestation in Bolivia. Asymptomatic congenital
pregnancies indicates the importance of larger studies on women with a history of congenital transmission.

**Intra-uterine infection and fetal sensitization** – The suggestion that intra-uterine infection with *T. cruzi* might induce the synthesis of anti-heart antibodies by the fetus during the fetal and perinatal period (Szarfman et al., 1975b) is now considered doubtful. However, this does not preclude the possibility that the passage of other humoral factors of maternal sera may lead to sensitization. *In-utero* sensitization via passively acquired maternal antibody should be considered as it has been observed in the offspring of a small sample of chagasic women in Brazil (Eloi-Santos et al., 1989). Cord blood mononuclear cells exhibited strong proliferative responses against idiotypes expressed on antibodies prepared from the mothers' serum, especially early pregnancy serum. This was the first preliminary experimental evidence that children born of mothers with chronic infections are born possessing anti-Id reactivity. This study, if confirmed in a larger sample, underlines the importance of a better understanding of maternal immune status during pregnancy and how this relates, not only to congenital infection, but also to disease susceptibility within population groups. The importance of maternal-fetal interactions is supported further by evidence of family clustering.

Family clustering of infection has been observed in an endemic area, and 10% (20/203) households had five or more seropositive individuals (Mott et al., 1976). The rate of seropositivity and median age of seropositives varied according to the serological status of parents. The authors suggested that the immunological response of children of seropositive mothers differed from that of children of seronegative mothers, and that various maternal-fetal immunologic interactions could account for this. Family clustering of cardiovascular disease was also observed in Goiânia, Central Brazil (Zicker et al., 1990). An association between a sibling history of heart disease and left anterior hemiblock was considered consistent with studies suggesting a genetic component in the determinant of Chagas' heart disease – but could also indicate maternal-fetal sensitization. Longitudinal studies in Castro Alves indicate that risk for development of heart disease is bimodal, with peaks at age 10-19 years and 30-39 years (Mota et al., 1990). The authors suggested that some individuals develop cardiac abnormality after a long latent period. Evidence that the age of onset of clinical disease is linked to *in-utero* sensitisation (or asymptomatic congenital infection) is speculative, but remains a possibility.

**CONCLUSIONS**

From the foregoing review it can be concluded that there are still many questions to be answered about the specific risks of infection in women, especially in pregnancy. To answer these would require a shift of emphasis to more epidemiological studies - perhaps an unlikely event with the current emphases on operational studies for improved vector control and basic immunological research (although this rarely includes the immunology of human pregnancy infection or the implications of sex differences). Even if vector control is successful, it will still leave a large reservoir of seropositive women, and the risk to the offspring of these women should be known. Moreover, congenital infection maintains a reservoir of infection and a transmission mechanism which continues after vector control. It has already contributed to the establishment of Chagas' disease as an urban, as well as a rural problem.

Congenital transmission tends to be regarded as an epidemiologically unimportant result of infection with *T. cruzi* but this is not the case. In the State of Bahia, Brazil, there is nearly one case of congenital infection per 1,000 babies and prevalence among migrant women from rural areas living in Salvador was 10.9% (Bittencourt et al., 1985a). The corresponding figures are much higher in Bolivia where maternal infection rates constitute a serious health problem. It is likely that much could be learnt about the factors predisposing to clinical disease if more attention were given to infection patterns in women -pregnant and non-pregnant.

**REFERENCES**


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