Immunologie de la reproduction : relation materno-fœtale
Reproductive immunology : materno-fetal relationship
G. Chaouat Ed.
Colloque INSERM, Vol. 154, 1987, pp. 297-302

MATERNO-FOETAL INTERACTIONS IN EXPERIMENTAL CHAGAS DISEASE

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Our laboratory is involved in a research programme studying relationships between mother and foetuses or new born in Trypanosoma cruzi infection. The Chagas' disease, due to T. cruzi is a major health problem, estimated to affect over 24 million people in latin america.

Different epidemiological studies indicate a mortality of 10% in the acute phase of the disease. After many years, 30 to 50% of the patients having survived of the acute phase suffer from cardiac or digestive pathologies, leading to hight level of morbidity and death. The remaining people are asymptomatic, even if they keep some degree of parasitic infection.

The reasons for these differences in susceptibilities are not known. Our hypothesis is that, in endemic areas, individuals born to infected mothers, could be subjected to a prenatal and/or postnatal maternal influence on their immune system.

Many works have studied congenital Chagas' disease, due to direct transmission of parasite from mother to foetus or newborn (found in 1.6 to 13% of seropositive mothers - 1,2). However no relevant information is available about other interactions between T. cruzi infection and pregnancy.

Consequently, we choose to work on experimental T. cruzi chronic infection, the most frequent clinical form of Chagas' disease, in four main directions studying : 1° the influence of pregnancy on infection (in mothers and their foetuses); 2° the influence of infection on pregnancy (reproductive capacity and foetal growth); 3° the immunological status of pregnant mice during infection; 4° the evolution of infection in mice born to infected mothers, i.e. the consequencies on offspring of the infection of their mothers.

1. Firstly, we showed that pregnancy did not modify the mouse T. cruzi chronic infection, since no mortality was observed and parasitemia were similar in infected and pregnant mice as in infected but not pregnant ones. Moreover, parasites were never found in foetal blood. In different studies, using hundreds of mice born to mothers with chronic infection, spontaneous mortality was never observed. Weekly blood examinations for parasites in offspring were always negative until 2 months after birth,

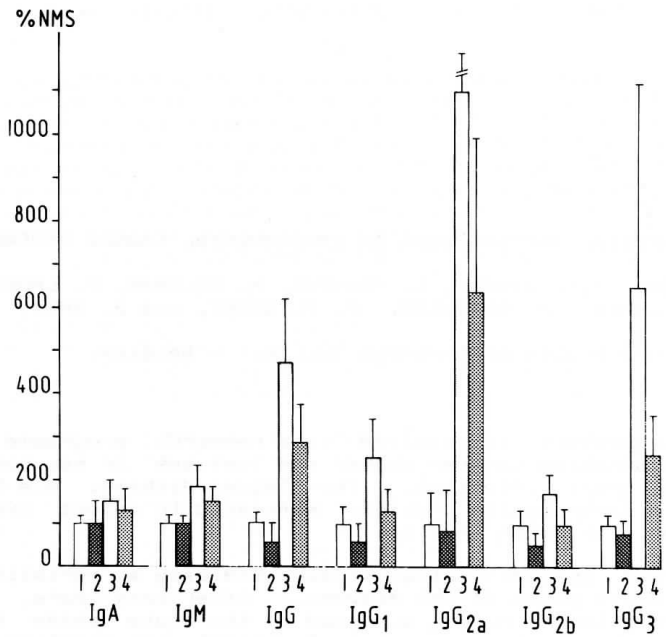

fig. 1. Immunoglobulin serum levels in mouse groups: control (1), pregnant (2), T.cruzi infected (3), T.cruzi infected and pregnant (4) (NMS = normal mouse serum)

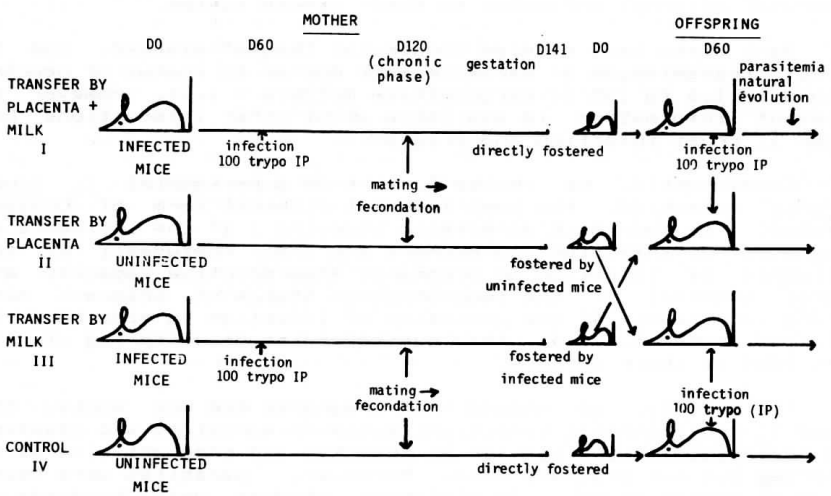

fig. 2. Experimental protocol to study the influence of maternal infection on the resistance to infection of adult offspring (BalbC mice; Tehuantepec strain of T.cruzi).

indicating absence of pre-/or postnatal infection in our model (3).

2. About the influence of infection on pregnancy, we showed that chronic T. cruzi infection had no influence on mouse reproductive capacity, since mating and fecondation rates, resorption, implantation and litter sizes were similar in pregnant mice, infected or not. However, foetal weights and forelimb ossification, considered as good foetal growth indexes, were shown significantly lower in infected and pregnant mice than in not infected and pregnant ones. This indicated an intrauterine growth retardation in T. cruzi infected mice, in absence of congenital infection (3).

3. Since pregnancy did not influence the parasitemia of the chronic infection, it was interesting to compare the immunological status of infected and pregnant mice with infected and non pregnant ones in order to observe if pregnancy-associated immunodepression was occuring.

The experimental protocol used four mouse groups: the first group is the control group non infected and non pregnant; the second one is only a pregnant group without infection; the third is an infected group but non pregnant; the fourth is infected and pregnant. Comparisons between groups 1 and 2 indicate the role of pregnancy on the immunological parameters, in physiological conditions without infection. Comparisons between groups 3 and 4 indicate the role of pregnancy on the same parameters during infection.

As shown in fig. 1, no differences are observed in the IgA and IgM levels, whereas important variations were seen in IgG. All IgG subclasses, were affected by pregnancy. Their levels decreased significantly by 40 to 60% compared with the non pregnant values. This included IgG2a and IgG3, the two subclasses known to be particularly high during infection (unpublished data, 4). The levels of circulating immune complexes and rheumatoid factor were less affected by pregnancy than anti-DNA antibody levels. Such parameters are also known to be high during infection, reflecting an important polyclonal B stimulation. Pregnancy had a low influence on the spleen weights. The specific anti-T.cruzi IgG antibody response showed a significant, but limited decrease by 20 to 30% due to pregnancy.

Briefly, we can summarize these results, saying that pregnancy, during T. cruzi chronic infection of the mouse, is associated with a partial decrease of levels of immunological parameters, but such decrease is not sufficient to modify the course of the mother's infection.

4. The fourth step of our work study the influence of maternal infection on the resistance to infection of adult offspring.

The experimental protocol is indicated in fig. 2. Balb/c mice were infected to establish a chronic phase of the disease. Mating took place during the chronic phase and the offspring were divided in different groups. One group of mice, born to infected mothers was fostered by infected mothers. Another group,

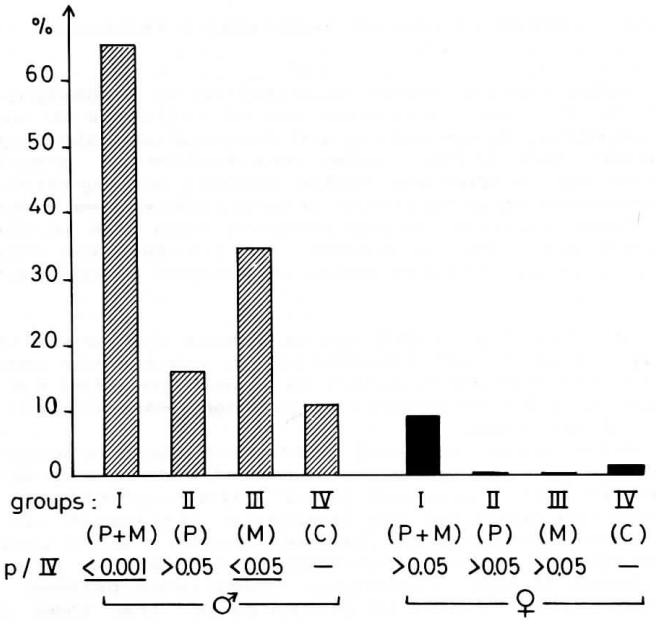

fig. 3. Maximal T.cruzi parasitemia in infected offspring from chronically infected mice (P = placenta; M = milk; C = controls)

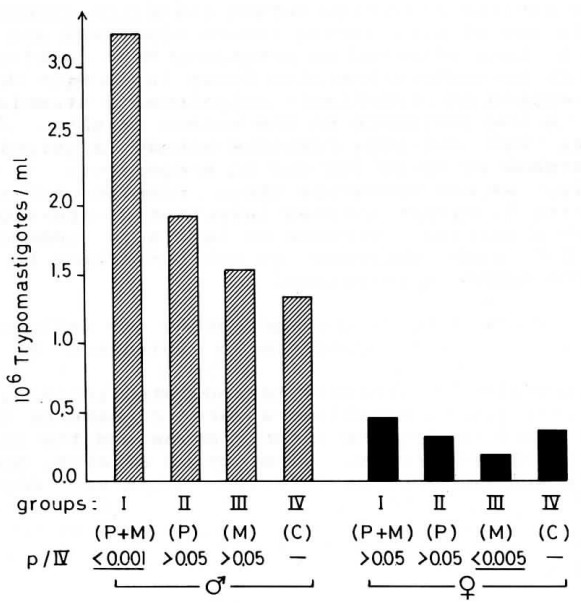

fig. 4. Mortality rates in infected offspring from chronically infected mice (P = placenta; M = milk; C = controls)

born to infected mothers was fostered by uninfected ones. The same was true for mice born from uninfected mice. So, we obtained four groups. One has been exposed to placenta and milk from infected mothers. The second to only placenta of infected mothers. The third to only milk and the fourth were controls. We infected the mice as adults, following the same protocol as for the mothers and we followed the natural evolution of infection by parasitemia and mortality rates.

Comparing parasitemia (fig.3), males of group 1 (born from and fostered by infected mothers) had a parasitemia significantly higher (3 times) than any other groups. However, in females such differences were not found. This is even more marked for the mortality rate of males which was six times higher than the controls (fig. 4). Such phenomenon in male mice could not be observed if offspring was infected by Schistosoma mansoni or Plasmodium chabaudi in place of T. cruzi.

These results indicate : 1° a very important decrease of resistance to T. cruzi infection in male mice, but not in females, born to infected mothers; 2° the absolute need for both pre and postnatal effects to produce this phenomenon, since only mice born to and fostered by infected mothers, were shown with a decreased resistance; 3° the phenomenon is specific of T. cruzi since it was not observed with other parasites. As far as we know, similar results have never been reported in T. cruzi infection.

The immunological aspects of this decreased resistance are under investigation. So far, preliminary results seems to indicate a defect only in antibody production of subclasses IgG2a and IgG2b. Spleen weights, spleen cell proliferations to mitogens or antigens, cell subpopulations were similar in all groups. Our present results indicate that some very important specific immune mechanism is impaired in this group and we try to identify it. We think that, if this effector mechanism is found, it might be very relevant in the protection against T. cruzi parasites.

In conclusion, such results highlight the unsuspected but important interactions between T. cruzi and pregnancy. If pregnancy decrease the levels of immunological parameters, it does not modify the chronic infection of the mother. However, clearly it impedes the foetal growth in absence of congenital infection. Morevoer, maternal infection has important effects on the evolution of the infection in offspring, at least on the acute phase of the disease, considerably increasing parasitemia and mortality.

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SUMMARY

If many works have studied congenital Chagas' disease, no relevant information is available about other interactions between T. cruzi infection and pregnancy. In order to clarify such relationships, works were performed using mice chronically infected by T. cruzi. The mouse reproductive capacity was not influenced by infection. However, a foetal growth retardation (studies of foetal weights and forelimb ossification), in absence of congenital infection, was observed in infected mice. Moreover, pregnancy, during T. cruzi infection was shown to be associated with a partial decrease of levels of immunological parameters (immunoglobulins, circulating immune complexes, rheumatoid factor, anti DNA antibodes) and of anti-T.cruzi antibodies, but such a decrease was not sufficient to modify the course of the mothers' infection. Finally, the influence of maternal infection on the resistance to infection of adult offspring was studied. Very important decrease of resistance to infection was observed in male mice but not in females, born to and fostered by infected mothers. This phenomenon was shown to be specific of T. cruzi. Immunological aspects of this decreased resistance are under investigation.

RESUME

Si beaucoup de travaux ont étudié la maladie de Chagas congénitale, aucune information n'est disponible sur les interactions entre l'infection à T. cruzi et la gravidité. Dans le but de clarifier ces relations, des études ont été réalisées avec des souris chroniquement infectées par T. cruzi. La capacité de reproduction des souris n'était pas influencée par l'infection. Cependant, un retard de croissance foetale (étude des poids foetaux et de l'ossification des membres antérieurs), en l'absence d'infection congénitale, était observée chez les souris infectées. De plus, la gravidité, pendant l'infection à T. cruzi, était associée à une diminution partielle des taux des paramètres immunologiques (immunoglobulines, immuncomplexes circulants, facteurs rhumatoïdes, anticorps anti-DNA) et des anticorps anti-T.cruzi, mais cette diminution n'était pas suffisante pour modifier l'infection de la mère. Enfin, l'influence de l'infection maternelle sur la résistance à l'infection de la progéniture adulte était étudiée. Une diminution très importante de cette résistance était observées chez les souris males, mais pas chez les souris femelles, nées et allaitées par les mères infectées. Ce phénomène était montré spécifique de T. cruzi. Les aspects immunologiques de cette diminution de résistance sont en cours d'étude.

ACKNOWLEDGMENTS

This work has been supported by the Belgian FNRS (Grant n° 1.5.603. 83F et 3.9003.87), ULB research fund, Belgian CST project n°18114 bis et 30191 and EEC (grant n° TSD M024B-RS).