

Pregnancy and Chagas Disease: Benznidazole's Impact on Pregnancy and Newborns: A Report of Four Cases

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Abstract. In recent decades and because of migration, Chagas disease has become a global public health problem. A significant focus has been placed on pregnant women who can transmit the disease to their offspring. Here, we report four cases of women who did not know that they were pregnant while they were being treated with benznidazole. A diagnosis was established according to serology and *Trypanosoma cruzi* polymerase chain reaction (PCR)–standardized tests. Treatment was discontinued when pregnancy was confirmed, and a thorough follow-up was carried out. Although each case was different, none of the mothers developed health problems during pregnancy, and their newborns were delivered without any teratogenic effects.

INTRODUCTION

American trypanosomiasis is a vector-borne infection caused by the protozoan parasite *Trypanosoma cruzi*,¹ although it may also be transmitted through blood transfusions or from mother to child during pregnancy.² There are two drugs currently available for its treatment, nifurtimox and benznidazole, launched in 1967 and 1973, respectively, which have been shown to be effective for treatment during the acute phase of the infection. Previously, there was no international consensus regarding the treatment of the chronic phase because of the high frequency of undesirable side effects and poor indications of an apparent cure.³ Despite this, in recent decades, drug treatment has been offered and benznidazole is considered the first-line therapy.^{4,5} The treatment of infected women of childbearing age prevents congenital infection,⁶ but the side effects of benznidazole discourage its use in pregnant women.⁷ However, no side effects have been reported during breastfeeding.^{8,9} For ethical reasons, there have been no high-quality studies regarding treatment in pregnant women (benznidazole was found to cross the placental barrier and bind to fetal proteins in experimental rat models in the early 1980s),¹⁰ and a strong recommendation not to treat during pregnancy is given in different guidelines.^{7,11,12} Therefore, guidance regarding effective contraception during benznidazole treatment should be given to women of reproductive age. A few cases of uneventful benznidazole treatment of acute Chagas disease during pregnancy have been reported.^{13–16} Our aim was to present four cases (part of our larger Chagas patients' cohort) of pregnant women (and their newborns) who were treated with benznidazole while they were unaware of their pregnancy.

PATIENTS AND METHODS

Patients were diagnosed with Chagas disease through two complementary methods: a chemiluminescent microparticle immunoassay (ARCHITECT Chagas[®], Abbott, Chicago, IL) and an indirect immunofluorescent assay (Inmunofluor

Chagas kit, Biocientífica S.A., Buenos Aires, Argentina). In addition, PCR was performed, as previously described, to search for the parasite in the peripheral blood.¹⁷

During the study period (2007–2017), more than 1,500 patients received benznidazole in our Tropical Medicine Out-patient Clinic. Four cases of women who did not know that they were pregnant when treated with benznidazole were analyzed according to our standard protocol.¹⁷

Patients were treated orally with benznidazole (100 mg) three times a day for 60 days.¹⁸ The cumulative dose did not exceed 18 g of benznidazole to prevent some of the known side effects, such as polyneuritis and bone marrow depression, as stated in previous reports.¹⁹ Side effects of benznidazole were considered to be present when women described any abnormal pregnancy symptoms or signs of common benznidazole side effects, including abdominal pain, rash, weight loss, headache, nausea, vomiting, low white blood cell count (neutropenia and eosinophilia), hives, itching, decreased appetite, hypersensitivity skin reactions, and diarrhea. Other events during pregnancy, such as anomalous findings by echography, high blood pressure, or unexpected hemogram parameters were also registered.

As part of our standard of care, before benznidazole administration, all patients were given advice regarding treatment, including information about Chagas disease, benznidazole doses, and possible side effects. They were also advised not to drink alcohol and not to eat spicy or fatty food, and in the case of childbearing age women, information to prevent pregnancy was provided. Women who were found to be pregnant during treatment were advised to stop medication, and information about the discontinuation of pregnancy was given.

RESULTS

Of the 1,580 treated patients, women represented more than half of the cohort (62.8%): 84.9% were of childbearing age (15–50 years) and 176 got pregnant during the study period, nearly all after finishing the treatment or without starting it. Nevertheless, four cases of unexpected pregnancy during benznidazole treatment were registered. All patients were from Bolivia (in our cohort, 93.9% of the women were from this country). The main characteristics of these women and their newborns are described in Tables 1 and 2.

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TABLE 1
Characteristics of pregnant women

Mother	Country	Age (years)	Years in Spain	Kuschnir*	Serology	Pretreatment PCR	Posttreatment PCR	Days of treatment	Pregnancy at discontinuation (weeks)	Treatment of adverse events	Incidents during pregnancy
1	Bolivia	27	6	I	Positive	Positive	Positive	20	5	No	No
2	Bolivia	38	5	I	Positive	Positive	Negative	30	10	No	No
3	Bolivia	15	10	I	Positive	Negative	Negative	60	4-6	No	No
4	Bolivia	31	4	0	Positive	Not performed	Negative	15	6	No	No

* Classification for Chagas cardiomyopathy.²⁰

Case 1 was a 27-year-old woman who had been living in Spain for 6 years. Asymptomatic Chagas disease was diagnosed (Kuschnir I and normal digestive study). The Chagas PCR was positive before treatment initiation; 20 days after being on benznidazole, she decided to discontinue treatment because of a positive pregnancy test. She was in her fifth gestational week. During pregnancy, no adverse events were reported. A second PCR test just before birth remained positive. Her child was born at full term, with no complications during spontaneous vaginal delivery, and no malformations or teratogenicity were found (weighed, 3.4 kg); however, *T. cruzi* PCR was positive, and both the mother and the newborn received a 60-day course of benznidazole. After that, the family returned to Bolivia, and there was no follow-up.

Case 2 was a 38-year-old Bolivian woman who had been living in Spain for 5 years diagnosis of asymptomatic Chagas disease was given because of a positive PCR test. After being on benznidazole treatment for 1 month, trypanocidal treatment was discontinued because of a 10-week pregnancy. After that, no adverse events were reported. A second PCR test just before delivery was negative. Her child was Caesarean-born at full term with no complications. The newborn was healthy, with no signs of teratogenicity. Although the serology test was positive in the first days of life, it became negative during the first year, and the *T. cruzi* PCR test was also negative. In the 6 years of follow-up, the child did not develop any relevant health problems.

Case 3 was a 15-year-old Bolivian female who had been living in Spain for 10 years. Chagas PCR was negative, and at the end of a 60-day course of benznidazole treatment, she discovered she was pregnant (fourth or sixth week of gestation). During her pregnancy, no adverse events were reported. Her child was born with no complications (vaginal delivery; weight, 3.4 kg). Neither genetic malformations nor teratogenicity was found. The serology test was positive in the first days of life, but became negative by the end of the first year of life. The Chagas PCR test was also negative at birth. In the three years of follow-up, no medical problems have been reported.

Case 4 was a 31-year-old Bolivian woman who had been living in Spain for 4 years. Chagas PCR was not performed, and the treatment was prescribed according to a positive serology test. After 15 days, benznidazole was discontinued

as she discovered that she was pregnant (fifth week). She decided to continue her pregnancy, and no adverse events were reported. A negative *T. cruzi* PCR was reported before delivery. Her child was born at full term without complications by vaginal delivery. The newborn was healthy, and the Chagas serology test was negative during the first year of life. The *T. cruzi* PCR was negative. In the 3-year follow-up period, the child did not develop any relevant health problems.

DISCUSSION

Approximately 1–10% of the infants born from infected mothers develop acute *T. cruzi* infection.²¹ It has been demonstrated that women who complete a course of benznidazole treatment before getting pregnant are able to prevent congenital infection.⁶ For this reason, treatment should begin as soon as infection is detected in women of childbearing age. At the same time, this drug should not be administered during pregnancy. Despite the recommendation to use contraception, some women may get pregnant during treatment, may realize this weeks after taking benznidazole, and may not want to discontinue their pregnancy.

Our four cases are unique. Each mother's disease course was different, illustrating four possible scenarios concerning pregnancy and simultaneous Chagas disease treatment.

In our cohort, two women (cases 1 and 2) tested positive for *T. cruzi* PCR before pregnancy. In case 1, having received only 20 days of treatment, the woman remained positive after delivery, and she transmitted the infection to her newborn. On the other hand, in case 2, the woman fulfilled a 30-day course of treatment, and her PCR was negative by the time of delivery; she did not transmit the infection to her offspring. These data make us consider the minimum duration of treatment necessary for a negative PCR test, therefore avoiding the risk of congenital transmission. Although some authors have focused on this topic, further studies are needed to provide clarification.^{22–26}

In our cohort, benznidazole was administered in the first trimester in three patients and during the second trimester in another case, having completed between 15 and 60 days of benznidazole treatment. However, benznidazole may be carcinogenic, teratogenic, and cause reproductive toxicity and/or genotoxicity. To investigate its teratogenicity in animal

TABLE 2
Characteristics of newborns

Children	Delivery	Prematurity	Teratogenicity	Congenital Chagas disease	PCR	Treatment	Follow-up (years)
1	Vaginal delivery	No	No	Yes	Positive	Yes	1
2	Caesarian	No	No	No	Negative	No	6
3	Vaginal delivery	No	No	No	Negative	No	3
4	Vaginal delivery	No	No	No	Negative	No	3

models, a single study has been performed since the approval of benznidazole. The results describe transplacental trespassing and covalent binding of its metabolites to fetus proteins.¹⁰ Although the analysis of teratogenicity was not the aim of this study, the potential risk of benznidazole could not be excluded. Some studies that have focused on nitroimidazoles (benznidazole's same structural family) report different data, either establishing the safety of the compounds or determining that members of this family may cause teratogenic effects in humans and mice during different stages of pregnancy.^{26–29}

In our series, in addition to the small sample size, the short treatment course undermines the reliability of definite conclusions about the effects of benznidazole on mothers and newborns. Previous reports describe cases in which the decision to treat was made based on the risk to the mother and/or fetus and concluded a positive risk/benefit balance.^{13–16}

With the current knowledge, we cannot propose treating pregnant women, but it is important to report any further experience with pregnancy and benznidazole that may provide additional information on this topic.

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