Cutaneous Leishmaniasis during Pregnancy: Exuberant Lesions and Potential Fetal Complications

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Cutaneous leishmaniasis affects millions of people worldwide. After observations of atypical lesions in pregnant women at the health centers of Corte de Pedra, Brazil, 9 years of records were reviewed, and 26 pregnant patients were identified. A retrospective case-control study revealed that lesions in pregnant women were much larger than those in nonpregnant patients in an age- and sex-matched group (mean area, 6.08 cm^2 vs. 1.46 cm^2; $P = .008$), and many lesions had an exophytic nature. Despite foregoing treatment until after delivery, response to pentavalent antimony therapy was favorable (rate of cure with 1 course of treatment, 85%). High rates of preterm births (10.5%) and stillbirths (10.5%) were reported. Cutaneous leishmaniasis during pregnancy produces distinct lesions and may have adverse fetal effects.

Worldwide, leishmaniasis affects >12 million people in 88 countries, with a yearly incidence of 2 million cases [1]. The majority of cases are cutaneous leishmaniasis (CL), which is most common in adolescents and young adults from rural areas of extreme poverty [2]—a population with a high fertility rate. Pregnancy is associated with improvement of most inflammatory diseases [3] and an increased susceptibility to many infectious agents, including *Malaria* species [4] and *Listeria monocytogenes* [5]. Moreover, during pregnancy, many infections are associated with adverse fetal outcomes [6]. In the case of leishmaniasis, infection with the viscerotropic form has been described during pregnancy, resulting in vertical transmission and fetal loss when treatment failure occurs [7]. After occasional observations of atypical CL during pregnancy, we retrospectively reviewed all cases of CL and mucocutaneous leishmaniasis (ML) seen at a reference center, identifying gravid patients (a standard screening question). We report clinical aspects of these cases, including lesion size and impact on pregnancy outcome. In addition, a retrospective case-control study comparing lesion size and response to therapy was performed.

Methods. The study was performed at the Corte de Pedra Reference Center for Tegumentary Leishmaniasis in Bahia, Brazil, which has been in operation for >20 years [2]. Yearly, >600 patients are treated for CL and ML at this center.

We manually reviewed charts for all patients with CL or ML who were seen at the referral center during the period 1997–2005, selecting patients who were pregnant and had signs of leishmaniasis. Cases were defined by inclusion criteria of a definite diagnosis of CL or ML as the combination of a compatible lesion and (1) biopsy results showing amastagotes or compatible histopathologic findings, (2) positive culture results from a lesion aspirate specimen, or (3) positive Leishmanin test results. Exclusion criteria were incomplete documentation of pregnancy or of postpartum follow-up. Control subjects were age-matched (within 5 years of age) and sex-matched; the 2 consecutive patients with definite leishmaniasis who were evaluated after each case patient were chosen as control subjects. Probable CL or ML was defined as a compatible lesion with lack of definitive test results.

At the initial visit, patient weight, lesion size and location, and the number of lesions were recorded, and past medical history was evaluated in a standard manner by 1 nurse. All women of childbearing age were evaluated for pregnancy. Leishmanin testing was performed at the initial visit. The initial lesion size was the size of the lesion recorded at the initial visit. The maximum lesion size was the size of the largest documented lesion. All patients found to be pregnant were followed up clinically without treatment for definitive leishmaniasis (i.e., pentavalent antimony compounds) until after delivery.

This study was approved by the Committee of Ethics of The Federal University of Bahia (Salvador, Brazil) and the institutional review board of Weill Medical College of Cornell University (New York, NY). Laboratory studies were performed in the university laboratory using standard commercial techniques. Histopathologic examination was performed in the pa-

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thology department. Slides were reexamined by 2 readers (D.R.F. and W.L.T.), who examined each slide for dermal and epidermal changes, the nature of the inflammatory infiltrate, and the presence of amastigote forms. The isolates were characterized at the *Leishmania* Collection of the Oswaldo Cruz Institute (Rio de Janeiro, Brazil) by multilocus enzyme electrophoresis, as described elsewhere [8].

Data were entered into Excel (Microsoft). Lesion areas were calculated as ellipses. The Mann-Whitney *U* test (Wilcoxon rank sum test) and Pearson rank test were performed using Stata, version 7.0 (Stata). $P < .05$ was considered to be statistically significant.

Results. We identified 27 pregnant patients among ~4200 people with suspicion of leishmaniasis. Of the 27 pregnant patients, there were 8 patients with probable leishmaniasis and 18 with definite leishmaniasis. One patient was excluded because of lack of postpartum follow-up information.

The characteristics of 26 patients with leishmaniasis during pregnancy are presented in table 1. Lesions appeared at a mean of 18-weeks gestation (95% CI, 13–21 weeks). Descriptions of vegetative, exophytic, or atypical lesions were found in 11 (42%) of 26 patient charts (figure 1). No manifestations of CL developed prior to pregnancy in any of the patients. Exophytic lesions were nonsignificantly correlated with trimester of pregnancy ($P = .338$, by Pearson rank test; $R^2 = 0.046$).

Lesions showed documented postpartum improvement in 3 patients prior to treatment; nonetheless, these patients subsequently received standard treatment (figure 2). Two patients (7.7%) initiated pentavalent antimony treatment during the first trimester but stopped treatment when pregnancy was discovered (after 7 days of treatment in 1 patient and after 13 days of treatment in the other patient). Both patients continued to have active lesions throughout their pregnancy, and neither woman had an adverse fetal outcome.

Nineteen patients provided information regarding pregnancy complications: 2 (10.5%) of 19 patients delivered preterm, 2 (10.5%) experienced a stillbirth, and 15 (79%) reported normal deliveries (table 1). Cutaneous lesions in patients who expe-

Table 1. Clinical and laboratory findings for 26 pregnant patients with probable and definite leishmaniasis, compared with findings for 36 nonpregnant control subjects with definite cutaneous leishmaniasis.

	Patients with cutaneous leishmaniasis	
Variable	Pregnant patients ($n = 26$)	Nonpregnant control subjects ($n = 36$)
Clinical finding		
Disseminated lesions[a]	3/26 (11.5)	0
Mucosal disease	2/26 (7.7)	0
Recurrent disease	2/26 (7.7)	0
Exophytic lesions documented	11/26 (42.3)	0
Week of pregnancy at lesion appearance (range)	18 (13–21)	NA
Treatment		
Glucantime		
One 20-day course	22/26 (84.6)	29/36 (80.5)
Two 20-day courses	2/26 (7.7)	7/36 (19.5)
Topical paramomycin	2/26 (7.7)[b]	0
No treatment	1/26 (3.4)	0
Azithromycin	2/26 (7.7)[c]	0
Fetal effects		
Preterm birth	2/19 (10.5)	NA
Stillbirth	2/19 (10.5)	NA
Reported normal birth	15/19 (79.0)	NA
Laboratory finding		
Positive culture result	7/11 (63.6)	3/7 (42.8)
Compatible biopsy result	11/11 (100)	4/4 (100)
Amastigotes	2/11 (18)	0

NOTE. Data are no. (%) of patients, unless otherwise indicated. NA, not applicable.

[a] Defined as >10 lesions.

[b] One patient subsequently received 1 course of glucantime therapy.

[c] Both patients received 1 course of glucantime therapy.

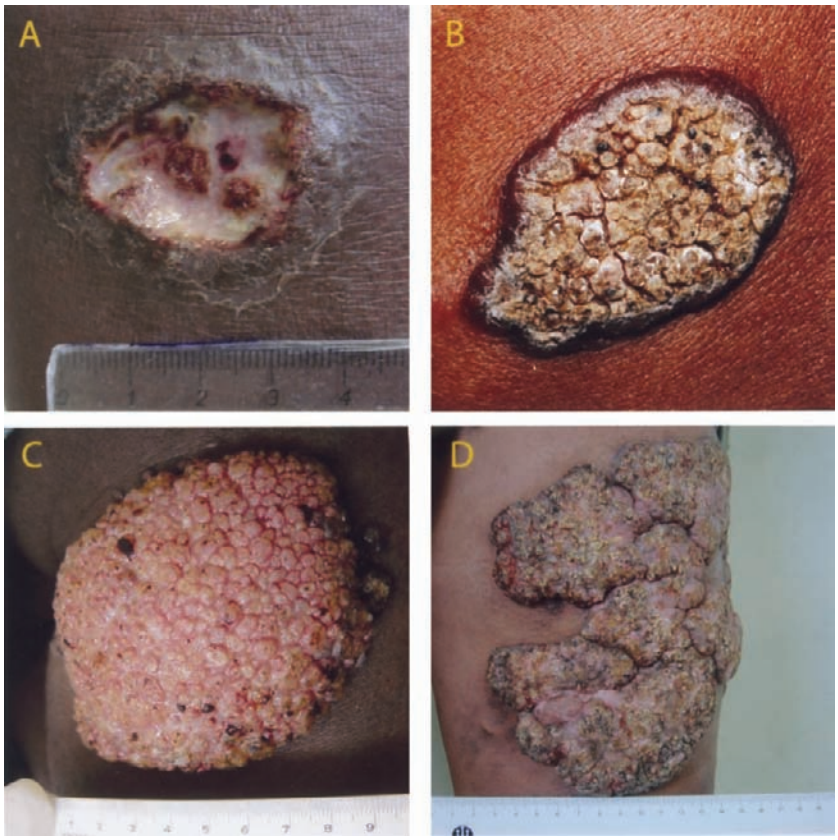

Figure 1. Appearance of cutaneous leishmaniasis during pregnancy. *A,* Typical, well-demarcated ulcer with raised borders on a patient's leg. *B,* Mildly raised, verrucous lesion on a patient's back. Massive, vegetative lesions on a patient's buttock *(C)* and thigh *(D).* Rulers represent centimeters.

rienced a preterm birth or stillbirth did not differ from those in patients who experienced normal deliveries with respect to clinical characteristics or trimester of onset of infection.

Biopsy specimens from pregnant individuals had an inflammatory exudate that was more intense than that typically found in CL, with a predominance of neutrophils, which is not typically observed. Culture results were positive for *Leishmania* species in 7 of 11 patients examined. Five specimens were no longer viable. Two specimens were typed as *Leishmania braziliensis* by multilocus enzyme electrophoresis.

Eighteen patients with definite leishmaniasis were compared with 36 age- and sex-matched control subjects. No difference was found between pregnant patients and nonpregnant control subjects with regard to the median size of the leishmanin delayed-type hypersensitivity test result (induration, 1.77 cm^2 [interquartile range (IQR), 1.13–2.53 cm^2] vs. 1.77 cm^2 [IQR, 0.86–2.98 cm^2]), median duration of lesions prior to the first visit (1.25 months [IQR, 1.0–2.0 months] vs. 1.0 month [IQR, 1.0–2.0 months]), median number of lesions (1.0 lesions [IQR, 1.0–2.0 lesions] vs. 1.0 lesion [IQR, 1.0–2.0 lesions]), and median number of treatment courses (1.0 course [IQR, 1.0–2.0 courses] vs. 1.0 course [IQR, 1.0–2.0 courses]). Both median initial lesion area (6.08 cm^2 [IQR, 1.88–12.01 cm^2] vs. 1.46 cm^2 [IQR, 0.79–3.78 cm^2]; $P = .008$, by Mann-Whitney *U* test) and median maximal lesion area (14.46 cm^2 [IQR, 5.50–54.95 cm^2] vs. 1.46 cm^2 [IQR, 0.79–3.78 cm^2]; $P < .001$, by Mann-Whitney *U* test) were significantly larger among pregnant women than among control subjects.

Discussion. This study demonstrates the influence of pregnancy on the clinical manifestations of CL in a region with *L. braziliensis* transmission. Patients who presented with CL while pregnant had much larger lesions than did nonpregnant women (median initial lesion area, 6.08 cm^2 vs. 1.46 cm^2), despite showing no difference in disease duration. Lesion size was also larger among our patients than among patients seen in a historical cohort from the same region who did not receive treatment (median lesion area, 4 cm^2; IQR, 3–5 cm^2) [9]. In contrast to the typical presentation of a well-demarcated ulcer with raised borders, lesions were frequently of a cauliflower appearance, which raised concern for other diseases, such as chromomycosis, yaws, or neoplasms. Although not previously reported, more-exuberant CL involving other species, including *Leishmania major,* has been observed during pregnancy in Northern Africa (H. Louzir, personal communication).

In a C57BL/6 mouse *L. major* model, larger CL lesions occurred during pregnancy, which correlated with decreased Th1

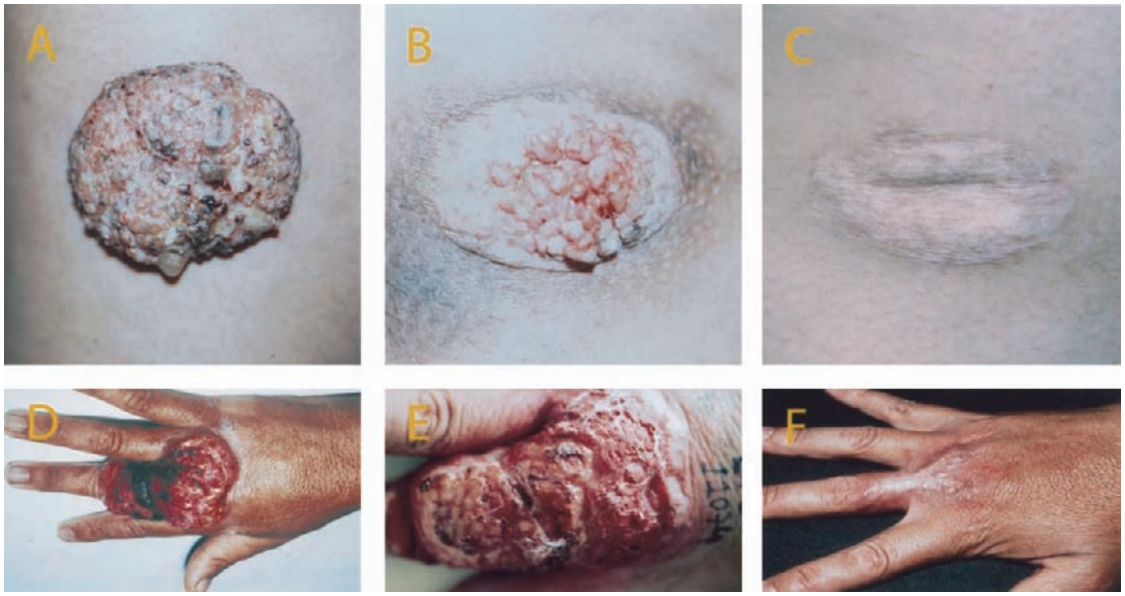

Figure 2. Spontaneous improvement of cutaneous leishmaniasis postpartum. Raised, atypical lesions seen during pregnancy *(A* and *D),* 1–2 months postpartum prior to treatment *(B* and *E),* and after 1 course of pentavalent antimony treatment *(C* and *F).*

cytokine production [10]. The human cell-mediated immune response is altered during pregnancy [11], with an overcompensation immediately after delivery. Because the main histopathological difference in lesions in pregnant women with typical lesions was increased, neutrophilic infiltration and fibrinoid necrosis, differential neutrophil signaling, or activation may play a specific role in development of atypical lesions.

Standard treatment of CL caused by *L. braziliensis* is 20 days of intravenous pentavalent antimony compound, which is potentially abortogenic. Because of this concern, only 2 patients received antimony during pregnancy (the 2 patients stopped treatment after they realized they were pregnant). Of note, these patients experienced full-term deliveries of healthy infants, although their lesions were not cured until after delivery. Because spontaneous cure has been reported to occur after delivery [9], the merit of different treatments cannot be evaluated. No patients in this study were cured while pregnant. No patients developed mucosal disease, although the small sample size limits its generalizations.

An unexpected finding was the high rate of preterm births and stillbirths. Various maternal infections, including malaria [4], listeriosis [5], and visceral leishmaniasis [7], are associated with fetal complications. In a murine model of CL, cutaneous infections increased the rate of implantation failure and fetal reabsorption [12]. In northeastern Brazil as a whole, infant mortality is high (~38 of 1000 infants die per year) [13]. The rates observed in this study are 3-fold higher than the normal rates for the region; however, the small size of this study limits conclusions regarding adverse fetal outcome.

This study is limited, because we did not measure the host immune response, including HIV seropositivity, which could modify disease presentation. In addition, our study was retrospective and, therefore, had no formalized protocol for treatment or data collection.

CL during pregnancy is characterized by larger lesions with a highly atypical, exophytic appearance. No therapy is known to cure disease during pregnancy, although postpartum cure has been found to be complete. CL during pregnancy has a notably different clinical presentation and may increase the risk of fetal complications. It is important for physicians who are caring for patients in regions where disease is endemic to recognize this presentation.

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