

Cutaneous Anergy in Pregnant and Nonpregnant Women With Human Immunodeficiency Virus

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ABSTRACT

Objective: To determine the prevalence of cutaneous anergy in pregnant and nonpregnant women who are seropositive for human immunodeficiency virus.

Methods and materials: The medical records of 159 women seropositive for human immunodeficiency virus were reviewed. Demographic characteristics and tuberculin skin test results were abstracted from the chart. Tuberculin skin testing was performed by the Mantoux method (5 tuberculin units of purified protein derivative injected intradermally). Anergy testing was performed using any two of the three following antigens; tetanus toxoid, mumps, or *Candida* skin test antigen. A positive tuberculin test was defined as induration of 5 mm or more, and a positive test for the other antigens was defined as any amount of induration over the skin test area. Anergy was defined as any amount of induration to the other antigens. A CD4+T lymphocyte count was obtained at the time of skin testing. Continuous variables were analyzed using the Mann Whitney—U test. Categorical data were analyzed with the chi-square or Fisher's exact test as appropriate. A two-tailed *P* value < 0.05 was considered significant.

Results: There were 102 nonpregnant and 57 pregnant women who returned to have their skin test results read. There was no significant difference in the prevalence of positive, negative or anergic skin test results between groups. The CD4+T lymphocyte count (mean ± standard deviation) in patients with anergic results was similar between pregnant ($375 \pm 256/\text{mm}^3$) and nonpregnant ($358 \pm 305/\text{mm}^3$) women (*P* = 0.64).

Conclusion: The prevalence of cutaneous anergy is similar among pregnant and nonpregnant women seropositive for human immunodeficiency virus. *Infect. Dis. Obstet. Gynecol.* 6:13–17, 1998. © 1998 Wiley-Liss, Inc.

KEY WORDS

TB skin testing; women; immunocompromised; HIV

A resurgence in the prevalence of tuberculosis (TB) has been observed since 1985 that has largely been attributed to the increasing prevalence of human immunodeficiency virus (HIV) infection.^{1,2} From 1985 through 1992, the number of reported TB cases increased 44% among persons aged 25–44 years, which was twice the rate observed overall in the United States during the same

period.³ These results indicated that TB may be an increasing problem among reproductive-aged women.

Presently in the United States, women account for the most rapid increase in the number of cases of HIV.⁴ These women are largely indigent minority women from large urban areas who are also at increased risk for TB. Indeed, a resurgence of ac-

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tive tuberculosis has been observed among reproductive-age women in endemic areas.⁵

Skin testing along with an anergy panel has been routinely used to screen for TB in HIV-positive patients. Cutaneous anergy is a risk factor for the development of TB and is more prevalent among HIV-seropositive than seronegative patients.⁶⁻⁸ Anergy also appears to increase as immune function declines.⁸⁻¹¹

The pregnancy state by itself has not been used to modify the criterion for defining a positive tuberculin skin test. However, the relationship between anergy and pregnancy is not well understood. Since CD4+T lymphocytes have been reported to decline steadily during pregnancy by some authors, it is theoretically possible that anergy would be more common in pregnant than nonpregnant women.^{12,13} Our objective is to determine the prevalence of cutaneous anergy among HIV-seropositive pregnant and nonpregnant women.

METHODS AND MATERIALS

The medical records of a cohort of HIV-positive women monitored at the University of Texas Women's Immunology Center, Houston, Texas, were reviewed between January 1, 1996, and January 31, 1997. All patients undergoing tuberculin skin testing had demographic characteristics, Centers for Disease Control (CDC) classification, and skin test results abstracted from the chart.

Skin test administration and reading were performed by trained staff. Tuberculin skin testing was performed by the Mantoux method; 0.1 ml of purified protein derivative (PPD) (tuberculin units per 0.1 ml Tubersol, Connaught Laboratories, Inc., Swiftwater, PA) was injected intradermally into the volar aspect of the right forearm. Anergy testing was performed using any two of the three following antigens: 0.1 ml of tetanus toxoid solution (5 limit of flocculation units per 0.5 ml of purified fluid [Ultrafined, Wyeth-Ayerst Laboratories, Philadelphia, PA]), 0.1 ml of mumps skin test antigen (40 complement-fixing units per 1.0 ml [Connaught Laboratories, Inc.]), or 0.1 ml of *Candida albicans* skin test antigen (ALK Laboratories, Wallingford, CT) administered similarly in separate sites on the volar aspect of the left forearm.

Readings were performed 48-72 hours following administration of the skin tests. The size of induration was measured with a flexible ruler. Erythe-

TABLE 1. Demographic data^a

	Nonpregnant (n = 102)	Pregnant (n = 57)
Age (years) ^b	28.2 ± 7.8	22.9 ± 5.3
Parity ^b	2.1 ± 1.7	1.3 ± 1.4
Ethnicity ^c		
Caucasian	7 (6.8%)	8 (14%)
African American	82 (80.4%)	42 (73.6%)
Hispanic	13 (12.8%)	6 (10.5%)
Other	0	1 (1.9%)

^aP < 0.005

^bData are expressed as the mean ± standard deviation.

^cNumber (%)

ma alone did not constitute a positive response. A positive tuberculin test was defined as induration of 5 mm or more, and a positive anergy test for the other antigens was defined as any amount of induration over the skin test area.¹⁴ Anergy was defined as any amount of induration to the other antigens.

Patients were excluded from skin testing if there was a history of tuberculin reaction of 10 mm or more verified in the patient's medical record, a history of a positive tuberculin reaction with treatment for TB infection or disease verified in the medical record, or placement of a tuberculin skin test seven days or less before the visit.

A blood sample for evaluation of lymphocyte subsets was drawn at the time the skin test was placed. Lymphocyte phenotyping was performed as lysed anticoagulated whole blood specimens by dual-color flow cytometry.

Statistical analysis was performed using a computer software package (True Epistat, Richardson, TX). Continuous data were analyzed using the Mann Whitney U-test. Categorical data were analyzed with the chi-square or Fishers' exact test as appropriate. A two-tailed P value <0.05 was considered statistically significant.

RESULTS

During the study period, 139 nonpregnant and 73 pregnant women received tuberculin skin testing. Thirty seven nonpregnant (26.6%) and 16 pregnant (22%) women did not return to have their results read. This left 159 women (102 nonpregnant and 57 pregnant women) for review.

Demographic data are shown in Table 1. Nonpregnant women were significantly older and of greater parity than pregnant women in this cohort, although this finding is unlikely to be clinically significant.

TABLE 2. Mantoux skin test results^a

	Nonpregnant (n = 102)	Pregnant (n = 57)
Positive	13 (12.7%)	5 (8.7%)
Negative	62 (60.7%)	37 (64.9%)
Anergic	27 (26.6%)	15 (26.4%)

^aP was not significant.

Eighteen (11.3%) of 159 women had positive tuberculin skin test results. Of these eighteen women with positive skin tests, two had positive chest X-rays. One patient had active TB, while the other had a right lower lobe pneumonia. Neither patient was pregnant. Both patients were treated with standard therapy. Forty-two (26.4%) of 159 women had anergic skin test results. All of these women had negative chest X-rays.

The CD4+T lymphocyte count (mean \pm standard deviation) was similar between pregnant (466 \pm 258/mm³) and nonpregnant women (456 \pm 279/mm³, $P = 0.76$). Tuberculin skin test results in pregnant and nonpregnant women are shown in Table 2. There was no significant difference in the prevalence of positive, negative, or anergic results between groups. Table 3 shows the CD4+ lymphocyte counts in patients with anergic skin test results. The CD4+T lymphocyte counts ranged between 8 and 1500 cells/mm³ among nonpregnant women and 27 to 760 cells/mm³ in pregnant women. However, there was no significant difference in the absolute CD4 count between groups using the current CDC classification. The CD4 count (mean \pm standard deviation) in patients with anergic results was similar between pregnant (375 \pm 256/mm³) and nonpregnant (358 \pm 305/mm³) women ($P = 0.64$).

DISCUSSION

The occurrence of tuberculosis among persons with HIV infection has prompted the development of guidelines for screening of TB. These guidelines include the recommendation that all HIV-infected persons receive a PPD tuberculin skin test (Mantoux test). Because of recent findings of anergy among asymptomatic persons with HIV, persons with HIV infection should also be evaluated for delayed-type hypersensitivity anergy in conjunction with PPD testing.¹⁵ These recommendations also include consideration of preventative therapy with isoniazid for anergic persons who are

TABLE 3. CD4+T-lymphocyte counts in patients with anergic skin test results^a

	Nonpregnant (n = 27)	Pregnant (n = 15)
>500/mm ³	5 (18.5%)	4 (26.7%)
200–499/mm ³	14 (51.8%)	5 (33.3%)
<200/mm ³	8 (29.7%)	6 (40%)

^aP was not significant.

known contacts of infectious tuberculosis patients and those from groups in which the prevalence of tuberculosis is >10%.¹⁵ Studies of parenteral drug users and homosexual men have observed an elevated risk for the development of active TB among anergic HIV-infected patients (2–12% per year).^{16,17} This risk substantially exceeds the estimated 10% lifetime risk for development of active TB in persons with a positive tuberculin test result and an intact immune system.

These recommendations also would apply to pregnant women, although historically most obstetricians have deferred chemoprophylaxis until after delivery. This is primarily due to reports of an increased risk of hepatotoxicity from isoniazid in pregnant women with anergy.¹⁸ Despite the risk of isoniazid hepatitis, some experts recommend that chemoprophylaxis be strongly considered after the first trimester for HIV-infected pregnant women with anergy.¹³

Although TB skin testing along with an anergy panel has been widely used, little information exists as to the prevalence of anergy among women, specifically during pregnancy. Studies have demonstrated that CD4+T lymphocytes decline during normal pregnancy by approximately 100 cells/mm³.^{12,13} Others have reported no difference in T lymphocyte subsets between HIV-infected and noninfected women.¹⁹ Since anergy has been shown to be indirectly proportional to the CD4+T lymphocyte count, pregnant women would theoretically be more likely to have anergic test results.^{8,15} This would potentially expose a greater proportion of pregnant women to chemoprophylaxis than nonpregnant women.

The overall prevalence of anergy in our study (26.4%) is lower than other large cohorts of HIV-infected persons. These studies primarily consisted of male homosexuals or parenteral drug users in which the incidence of anergy ranged from 36 to 63%.^{7,8,11,20} Unexpectedly, we did not observe any

difference in the prevalence of anergy between pregnant and nonpregnant women. Although the CD4+T lymphocyte counts were on average 100 cells/mm³ lower in the women with anergy, there was no significant difference in the CD4 count between pregnant and nonpregnant women. Our results differ from those of Mofenson's and coworkers, in which anergy was more common in nonpregnant (38/78, 49%) than pregnant (14/46, 30%) women.¹³ These results may be explained by the lower CD4 count seen in the nonpregnant patients in their cohort.

Previous studies^{8,11,15} have shown an inverse relationship in the prevalence of anergy as compared with the CD4 count. The prevalence of anergy ranges from 72 to 80% in patients with fewer than 200 CD4 cells/mm³.^{7,15} This is in contrast to our results in which 14/42 (33%) of women with anergic results had a CD4 count less than 200 cells/mm³. The wide range of CD4+T lymphocyte counts in our population confirms other investigators observations that an absolute CD4+ count does not reliably predict anergic test results.¹⁵

Although current CDC guidelines recommend consideration of chemoprophylaxis in anergic patients, others question the value and reliability of testing for anergy.^{20,21} This is because no gold standard is available to define the anergic state, and the performance of tests for detecting anergy cannot be evaluated in a conventional manner. Although observational data supports the conclusion that certain HIV-infected people with anergy are at high risk for active tuberculosis, until recently no data existed as to the benefit of providing chemoprophylaxis to this population. In a recent randomized double-blind controlled trial, Gordin et al. did not show a reduction in the incidence of tuberculosis in HIV-infected patients with anergy who received chemoprophylaxis with isoniazid.²² Although the results of Gordin's study do not support the use of chemoprophylaxis for anergic HIV-infected patients, consideration must be given to the risk of hematogenous transmission of TB to the fetus.

In summary, despite the observed decrease in the CD4+T lymphocyte counts, pregnancy did not alter the prevalence of cutaneous anergy in our population of HIV-infected women. Questions regarding the reliability of anergy testing and the apparent lack of benefit of chemoprophylaxis for

these patients should prompt reconsideration of routine anergy testing of the HIV-infected patient.

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