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Uterine cervix Nitric Oxide and Human Papillomavirus Infection in Women
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Abstract

The human uterine cervix produces nitric oxide, which participates in the regulation of immunological reactions. Nitric oxide also appears to play a role in carcinogenesis and in the progression/regression of precancerous lesions. The cervix is a target for human papillomavirus (HPV) infection, the most common genital infection, and this virus is necessary in the connection with precancerous and cancerous lesions of the cervical epithelium. Local factors, such as nitric oxide, may have a role in defense against HPV infection and/or in the results of HPV-induced cellular changes.

The levels of nitric oxide measured by those of its metabolites (NOx) in cervical fluid were compared in women with and without HPV, and different cytological and histological changes. Altogether, 801 women on 1033 occasions were studied. The effects of other relevant gynecological infections on cervical NOx levels were assessed independently and in association with high-risk HPV. Moreover, the expression of nitric oxide-producing endothelial (e) and inducible (i) nitric oxide synthase (NOS) in cervical epithelium was determined by Western blotting and immunohistochemistry.

In women with cytology suggestive of HPV infection, the levels of cervical fluid NOx were two-fold greater than in women with normal cytology. A similar difference was seen in NOx levels between women with (median 47.1 µmol/l) and without high-risk HPV infection (median 23.8 µmol/l). Cervical dysplastic lesions were associated with elevated levels of cervical fluid NOx; the women with low-grade lesions appeared to have the highest cervical nitric oxide production.

Chlamydia trachomatis infection was associated with elevated NOx levels. Neither bacterial vaginosis nor candida infection affected cervical fluid NOx levels, but the number of women with these infections was limited.

Cervical expression levels of eNOS and iNOS were higher in women with high-risk HPV infection compared with those without. Endothelial NOS was localized to vascular endothelium, while iNOS was mainly detected in the basal layer of squamous epithelial cells.

To evaluate the clinical significance of these findings, high-risk HPV-infected women without any treatment were followed for 12 months. At baseline, cervical fluid NOx levels were higher

in women with persistent high-risk HPV infection compared with those with eradicated high-risk HPV infection. Baseline NOx levels over the 75th percentile (87 µmol/l) predicted high-risk HPV persistence (odds ratio 4.1). This NOx cut-off value showed 33% sensitivity and 90% specificity for prediction of high-risk HPV persistence.

In conclusion, HPV infection was related with elevated levels of cervical fluid NOx as a result of activated expression of eNOS and iNOS proteins. High cervical fluid NOx levels were associated with high-risk HPV persistence, though the low sensitivity of this test to identify women with persistent high-risk HPV limits its clinical use.

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