RELATIONSHIP AMONG BACTERIAL VAGINOSIS, LOCAL INFLAMMATORY RESPONSE AND PRESENCE OF CERVICAL INTRAEPITHELIAL NEOPLASIA IN WOMEN WITH AND WITHOUT HUMAN PAPILLOMA VIRUS INFECTION

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Objective
An assessment of influence of human papilloma virus (HPV) infection on the presence of dysplasia and relationship among the local immune system, HPV infection and bacterial vaginosis (BV).

Methods
The study group (n = 143) was divided into: experimental arm: positive HPV-DNA sequence with polymerase chain reaction method on the cervix tissue specimen (HPV group, n = 82), control arm: negative HPV-DNA sequence (nHPV group, n = 61). Secondarily, the study group was divided into: subgroup with malignant lesions (ML group, n = 95) and subgroup with benign lesions (BL group; n = 48). Each patient was evaluated for: bacterial morphotype (Nugent score), cervical inflammation, HPV cervical infection classified by virus subtype, histopathological examinations of the cervix biopsy.

Results
In HPV group there was higher prevalence of women who: had their first sexual contact between 16 and 22 years (P < 0.001), had more than 3 previous or actual sexual partners (P < 0.001, P < 0.05; respectively), were unmarried (P < 0.01). We found: significantly higher prevalence of polymorphonuclear cervicitis and Candida albicans (C. albicans)-hyphae predomination in HPV group, but Gardnerella vaginalis in nHPV group, predomination of benign lesions in nHPV group, prevalence of Trichomonas vaginalis, as well as normal vaginal flora in BL subgroup, but C. albicans -sporae in ML subgroup. The most frequent infections in HPV group were those with HPV type 16 and 53.

Conclusion
The local inflammatory response is predominantly expressed by mononuclear infiltration in HPV presence, probably as a result of declined local immunity. In these circumstances, the commensalisms (i.e., C. albicans) flourish.

Keywords: Bacterial vaginosis; Cervical intraepithelial neoplasia; Humanpapilloma virus; Active immune response
anaerobes could act with a production of neoplastic change, or as a synergic agent with some viral agent. Some more recent studies also investigate the possible biochemical mechanism by which microorganisms might influence expression of oncogenic human papilloma virus (HPV). McNicol et al. [4] found that presence of Lactobacillus species, like (Döderlein bacillus) and E6 oncogene were associated with low-grade CIN or normal histology. It is generally considered that the mutations observed among the cancer genomes are a consequence of the survival selection caused by the surrounding microenvironment. Loss of class-I human leukocyte antigen (HLA) alleles under the selective pressure of anti-tumor cytotoxic T lymphocyte responses has been demonstrated in cell lines obtained from metastatic melanomas [5]. Alternated HLA phenotypes implicate the possibility of tumor immune escape from T-cell recognition in human cancer models. In human cervical cancer, local immunity against this HPV-associated neoplasia has been signified. However, this possibility of tumor immune escape from immunocytes recognition, and T-cells residing within the tumor milieu remain to be clarified. Sheu et al. [6] demonstrated that human cancer cells may alter the functional composition of anti-tumor effector-cells, including CD8 cytotoxic T-cells in the human cancer microenvironment. The immunoregulatory effects of cancer HLA genetic alterations in associated HPV in the human cancer milieu remains to be stratified. Tsukui et al. [7] reported that helper T-lymphocyte response, particularly interleukin (IL)-2 production to HPV antigens was greater among women with normal cytology than in women with different degrees of cervical neoplasia. de Grujill et al. [8] reported that T cell proliferative responses to HPV-16 E7 peptides correlated with persistence of HPV infection, but antigen specific IL-2 production was associated with both virus clearance, as well as progression of cervical lesions. A better understanding of tumor responses is needed to design future strategies for effective immune-prevention of HPV-associated malignancies. A common clinical management includes excisional treatment. However, a significant number of patients experience recurrence, but a clear understanding do not exists at the presence regarding the role of the immune system and its relationship with this disease recurrence. Our intention was to establish a prospective, controlled study with due regard to the presence of HPV whether there is a relationship between BV and CIN as this would mean a major shift in cervical screening practice, and giving some contribution to future understanding of possible relationship among the local immune system, present HPV infection and CIN.

Material and Methods

1. Eligibility criteria for participants
   For experimental group: presence of cervical HPV infection; for control group: absence of this infection.

2. The setting, location and timing where and when the date were collected
   The Department for Urogynecology and Pelvic Floor Disorders in the Clinic of Gynecology and Obstetrics, Medical Faculty in Skopje in the period from the 1st of January 2009 to the 1st of January 2010, according to the CONSORT statement [9].

3. Precise details of the interventions for each group, how and when they were actually administered
   The whole study group (n = 143) was divided into two subgroups: 1) The experimental arm: positive finding of the HPV DNA sequence with PCR method on the tissue specimen of the cervix (HPV group) (n = 82); 2) The control arm: negative finding of the HPV DNA sequence with polymerase chain reaction (PCR) method on the tissue specimen of the cervix (nHPV group) (n = 61). Secondarily, the whole study group was divided into another two subgroup according to the histology: 1) Subgroup with malignant lesions (ML) (n = 95); and 2) Subgroup with benign lesions (BL) (n = 48). The study was approved by the Local Research Ethics Committee of the Association of Gynecologists and Obstetricians of Macedonia.

4. How sample size was determined and the method used to generate the allocation sequence, including details of any restriction
   Every outpatient admitted at our Department for Urogynecology for routine control in abovementioned period, assessed for eligibility for this study (n = 168). Nine patients were excluded because they refused to participate. Additional 16 patients dropped out because they had invalid smears for cervical inflammation evaluation, i.e. no identifiable for cervical mucus smears. So, 143 patients were randomised and they completed the study. Eighty-two of them were positive of HPV infection and were included in experimental HPV group, but other 61 patients were negative of this infection and were included in control nHPV group. All subjects were given an explanation of the study and written informed consent was obtained. This was a controlled trial with no allowance for patient preference.

5. Specific objectives and hypotheses
   The purpose of the study was an assessment of: 1) The influence