Sex and Shedding of Human Immunodeficiency Virus

To the Editor—By distinguishing between women who ovulated during the menstrual cycle and those who did not ovulate, Greenblat et al. [1] found that sex, contrary to generally accepted opinion, influences circulating human immunodeficiency virus (HIV) type 1 RNA levels. In ovulating women, the virus load fell during the early follicular phase through the midluteal phase. Furthermore, cervicovaginal shedding of HIV among pregnant women was higher than it was among nonpregnant women with more-advanced HIV disease [2]. Since the hormonal balances of pregnant and nonpregnant women differ, the effects of ovulation and of pregnancy on HIV RNA levels seem to point to a connection with reproductive hormones. However, the mechanisms of both phenomena are not wholly understood. It may, therefore, be of interest to investigate similar phenomena in animals.

In sheep infected experimentally with Chlamydia psittaci, shedding of the microorganism occurs only during the periovular phase of the estrous cycle [3]. Detectable levels of chlamydiae obtained by vaginal swabs collected during different stages of the ewe’s estrous cycle were restricted to the day of ovulation until ~4 days later. Of note, a persistent chlamydial infection of the ewe’s reproductive tract occurred after the experimental infection. The periovular, increased shedding of C. psittaci in sheep and the influence of ovulation in women on the fluctuation in plasma HIV RNA level [1] seem to support the significance of changes related to reproductive ability.

Another comparison relates to birds. In some of 19 orders of birds examined over 4 years in Israel, shedding of C. psittaci was higher in the summer than it was in the winter [4]. A more-detailed follow-up was done in pigeons (Columbia livia domestica) during 12 consecutive months [5]. Examination by immunofluorescence of cloacal swabs revealed that C. psittaci affected a large percentage of these birds without causing clinical symptoms. Chlamydial shedding reached a nadir in December, increased regularly until it peaked in August, and then decreased, again reaching a low near December, thus demonstrating an annual cycle. The seasonal variations of chlamydial antibodies in the pigeons were similar to the seasonal variations of the shedding of the C. psittaci microorganisms, which also peaked in July–August.

The ubiquitous synchronizer of cyclic variations is the photoperiod [6]. Among vertebrate animals, the most highly evolved photoperiodic mechanisms occur in birds and regulate central life functions, including migration, reproduction, and molt [7]. In pigeons, for instance, size of the gonads increases during the part of the year when the length of daylight exceeds that of darkness. Although the increased shedding may be a consequence of increased reproductive ability, the same factor may stimulate gonadal growth and increase antibody levels and chlamydial shedding. The difference between the 2 mechanisms can be tested in the laboratory and may give clues to unknown factors that enhance the transmission risk by cervicovaginal shedding of infectious agents.

The common feature of the influence of ovulation on cervicovaginal shedding of microorganisms in women and sheep may deepen our insight into the mechanism of ovulatory activity by experimental studies of persistently infected ewes. The common feature of shedding of microorganisms in women and birds may differentiate between a direct effect of the increased size and activity of the reproductive organs and an indirect endogenous or environmental effect that stimulates the reproductive organs and increases shedding. Finally, a priori common stimulating effects in humans and animals cannot be excluded. Just as among vertebrate animals the most highly evolved photoperiodic mechanisms occur in birds, among mammals reproductive activity is most strictly regulated by light-dark changes in northern sheep [8]. Recently the idea that there is an endogenous clock mechanism in mammals, including humans [9, 10], was strengthened dramatically by the cloning of clock genes. The photoperiod or other environmental stimuli also synchronize these human clock mechanisms.

In conclusion, the mechanisms that lead to changes in cervicovaginal HIV shedding may be studied experimentally in sheep infected by C. psittaci and by investigating chlamydial shedding in pigeons exposed to different light regimens.

Philip Cohen
Veterinary Epidemiologist, Qiryat Tivon, Israel

References

Reprints or correspondence: Dr. Philip Cohen, P.O. Box 1170, 36 Hashedkedim St., Qiryat Tivon, 36501, Israel (cp@internet-zahav.net).

The Journal of Infectious Diseases 2000;182:375–6 © 2000 by the Infectious Diseases Society of America. All rights reserved.

0022-1899/2000/18201-0056$02.00
2000 by the Infectious Diseases Society of America. All rights reserved.

Reply

To the Editor—We appreciate the interest of Cohen [1] in our study of the effect of ovulatory status on virologic and immunologic markers in human immunodeficiency virus (HIV)-infected women [2]. The modulation of immunologic function in women by ovarian hormones remains an enigmatic topic that recently has occupied our attention. It was both curious and informative to read Cohen’s description of seasonal regulation of immunologic responses in other vertebrates, particularly in avian species. Although the periodicity is annual rather than monthly, seasonal susceptibility to chlamydial shedding in birds also reflects hormonal cues. It may be of interest to Cohen and others that ascending chlamydial infection in young women also reflects reproductive endocrinologic effects.

Most women with genital infections with Chlamydia trachomatis experience the onset of disease within 1 week from the first day of menses, a time when circulating progesterone levels are at a nadir and the estrogen-to-progesterone ratio is highest. In women with Chlamydia infections, those who develop pelvic inflammatory disease are less likely than control subjects to use progestin-dominant oral contraceptives [3]. A precedent for selective hormonal influence on upper genital tract infection has been established by using a guinea pig model of chlamydial infection. Guinea pigs were infected intravaginally with the chlamydial agent of guinea pig inclusion conjunctivitis, at various times during the estrous cycle [4]. Genital tract tissues were collected 30 days after infection and were processed for histopathologic analysis. No difference was seen in the course of lower genital tract infection. However, a significantly greater percentage of tissues from animals infected on day 11 of the cycle had chronic inflammation and fibrosis in the mesosalpinx, compared with those from animals infected on day 16 (~1 day after ovulation). The preovulatory endocrine milieu on day 11 of the estrous cycle corresponds to a condition of tonic estradiol such as that observed in the midfOLLicular phase of the human ovulatory cycle. These data indicate that hormonal conditions that manifest gestational effects, such as the midluteal phase in women, might be associated with lower HIV titers and the relative inhibition of chlamydial spread.

Other recent studies have demonstrated gender effects on the courses of tuberculosis and hepatitis [5]. Further studies are needed to extend our preliminary findings and define the apparent endocrine influences on susceptibility to infection in ovulating women. The manipulation of ovarian hormone production might play an important role in future measures to alter risk of infection or outcomes of infectious diseases.

Robert N. Taylor and Ruth M. Greenblatt
Departments of Obstetrics, Gynecology, and Reproductive Sciences and of Medicine, Epidemiology and Biostatistics, University of California, San Francisco

References


Detection of Cytomegalovirus Late (pp150) Antigen in Peripheral Blood Leukocytes of Patients with Human Immunodeficiency Virus–Related Lymphoma

To the Editor—We read with great interest the study by Boivin et al. [1], who reported on the expression, as determined by use of reverse transcription–polymerase chain reaction (RT-PCR), of late (pp150) cytomegalovirus (CMV) transcript in peripheral blood leukocytes (PBLs) of patients with AIDS. The authors found an association between pp150 expression and a high number of CMV DNA copies in PBLs, a positive CMV PCR assay in plasma, and the presence of CMV disease.

Detection of the expression of pp150 transcript by RT-PCR [2–3] and detection of the pp150 protein by monoclonal antibodies by using indirect IFA [4–6] have been demonstrated in granulocytes, monocytes, and lymphocytes from the blood of immunocompromised viremic patients. CMV disease is a common complication in patients who have human immunodeficiency virus (HIV)–associated lymphoma and low CD4 cell