Hormonal markers of susceptibility to sexually transmitted infections: are we taking them seriously?

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BMJ 2001;323:394–5

When the body is invaded by pathogens, each individual reacts with a battery of non-specific and specific immune defence mechanisms. Sex hormones play an important part in the host's resistance to sexually transmitted infections. This is shown by sex differences,[1] variations in detection of infection according to phase of the menstrual cycle,[2] increased susceptibility during pregnancy,[3] and evidence that use of hormonal contraception predisposes to infection.[4 5] The mechanisms by which specific sex hormones modulate the immune system have been reviewed.[6] This is a complex subject, and it is unfortunate that, in spite of its potential importance, no clear message about sex hormones has emerged or been harnessed to the development of strategies for controlling infection. This paper revisits some of the evidence that hormonal status influences susceptibility to sexually transmitted infections, especially in adolescents, and considers the practical implications of this evidence.

Summary points

- Sex hormones influence susceptibility to sexually transmitted infections, especially in adolescents
- Anatomical differences do not adequately explain sex differences in the epidemiology of genital herpes and HIV infection
- The host's hormonal status, rather than high risk sexual behaviour, may govern the course of infection after a primary exposure to chlamydia or human papillomavirus
- Menstrual irregularities indicate hormonal disturbance in adolescent girls
- Strategies for preventing infection could be improved if the actions of sex hormones were better understood

Sex differences

The best example of sex differences in rates of infection and disease for various sexually transmitted viral infections is genital herpes. Many studies report a higher seroprevalence of genital herpes in women than in men in both developed and developing countries,[7 8] after exposure has been controlled for,[9] and in every age group.[8] Among women who were initially seronegative, a higher risk of symptomatic infection and a faster rate of acquisition of herpes simplex 2 virus compared with men was shown in a well designed cohort study.[10] Sex differences were also striking in recent vaccine trials, with the vaccine showing limited protective efficacy against genital herpes for women but not for men.[11]

These sex difference were not attributed to sex hormones but to anatomical differences that are thought to make it easier for the virus to pass from men to women than vice versa.[12] According to this theory, in women the virus sits in a fluid filled cavity, which facilitates its transmission or, after vaccination, its exposure to neutralising agents. The same theory is used to explain sex differences in age of onset and seroprevalence of HIV infection. However, two analyses using population based data challenge this theory as an explanation for sex differences in prevalence by showing that epidemics of HIV infection are fuelled by high rates of transmission of virus from women to men.[13 14] From a biological perspective, pooling of virus in the vagina may be insufficient to establish infection. In an animal model of the human vaginal epithelium, oophorectomised female macaques treated with progesterone became infected after challenge with intravaginal simian immunodeficiency virus. This was attributed to thinning of the vaginal epithelium by progesterone.[15] In women, a number of studies have shown that hormonal contraceptives are associated with increased shedding of HIV in cervical and vaginal secretions,[1] which would also make women more likely to pass the virus to men than vice versa. These important observations are now being more rigorously tested in two multicentre randomised controlled trials.[16]

Biological immaturity—hormonal factors during adolescence

Satisfactory explanations of why adolescent girls have a higher prevalence of chlamydia and human papillomavirus infection than adult women, adolescent boys, and men have also proved elusive.[17 18] Compared with young women, young men have not been well studied, but infection rates are generally highest in men in their twenties. One common explanation for sex differences is that adolescent girls are highly susceptible to sexually transmitted infections because they are biologically immature. Yet, with the exception of some studies on cervical ectopy and use of hormonal contraceptives, biological factors have been little investigated.[4 5 19] Ectopy is difficult to measure and, when present, difficult to interpret. Sexual activity accelerates a reduction in ectopy, as shown in one cohort study in which HIV was more often found in adolescents with a mature cervix.[19] Explanatory models and risk profiles generally focus on sexual behaviour.

High risk sexual behaviour is an important determinant of an initial infection rather than a subsequent or persistent one. This was the conclusion of a cohort study of adolescents being retested for incident human papillomavirus infection.[20] Several large retrospective and prospective studies have failed to identify

consistent behavioural risk factors (for example, number of lifetime partners or use of condoms) that predict reinfection with *Chlamydia trachomatis*.[21 22] Reinfection studies are important because individuals who have multiple exposures are thought to be at much higher risk of disease.[17] Increased susceptibility to both initial and subsequent infection may be associated with use of hormonal contraceptives, but the data are not consistent enough to allow firm conclusions to be drawn.[23]

Many adolescents have primary infections. Immune status or hormonal status at the time of first infection could be an important determinant of rates of clearance or persistence of infection. Sex hormones regulate the function of several distinct compartments of the reproductive system, but many of the mechanisms that enhance resistance to sexually transmitted infections, such as cervical mucus production or ectopy, are synchronised through the menstrual cycle. Unstable hormonal profiles are the hallmark of adolescence, because sexual maturation is not complete until several years after menarche.[24] Relatively low concentrations of oestrogen are characteristic, and about a quarter of girls will have polycystic ovaries. Menstrual cycle irregularities are common in girls living in developed and developing countries (unpublished observations). Menstrual patterns are also disturbed by eating disorders, undernutrition, erratic ingestion of oral contraceptives, and periodic use of emergency contraceptives.

Prevention strategies

A better understanding of hormonal factors could be applied to preventive strategies in several ways. Firstly, menstrual irregularities are the most readily identifiable indicator that hormonal function, and hence immunity, may be disturbed. However, sensitive urine tests for hormones are now available and could be used to develop and validate markers of hormonal status to incorporate into algorithms for chlamydia screening. Recommendations in the United States are to routinely screen all sexually active women aged 25 years and younger for chlamydia at intervals of 6-12 months.[25] This seems an expensive approach given that current data show that only about a fifth of adolescents are reinfected within a year.[21 22]

Secondly, future vaccines against genital herpes may prevent disease but not infection, and adolescents may be a target group for vaccination. Evidence that efficacy may be specific to sex means that the vaccine needs to be tested in adolescent girls and women with well described hormonal profiles.

Finally, the benefits and disadvantages of hormonal contraceptives are likely to vary according to type of infection and contraceptive formulation. If the risks associated with different hormonal preparations were well described, contraceptive advice could be tailored to an individual or a population.

Funding: Max Elstein Fund.

Competing interests: None declared.

JEZ COULSON/INSIGHT

Adolescents may be a target group for vaccination against genital herpes

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(Accepted 17 May 2001)