Influence of ovarian hormones on urogenital infection

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Numerous studies have examined the influence of hormones on infectious diseases and there is now a wealth of data relating to the more specific effect of the sex hormones, oestrogen and progesterone, on urogenital infections. The interaction between these hormones and the immune system is complex and the variation of hormonal effect between species further complicates the true picture as related to humans. Although it is difficult therefore to draw general conclusions regarding predominant effects of specific hormones, there is the suggestion that oestrogen enhances the pathogenicity of many urogenital micro-organisms. Our understanding of the influential role played by sex hormones in disease pathogenesis is at an early stage and illustrates well the importance of drawing together and interpreting as a whole both epidemiological and molecular studies.

(Keywords: oestrogen; progesterone; urogenital infection)

The interaction between the immune system and the endocrine system has been the focus of much attention in recent years. This review will consider just one aspect of the endocrine system, the sex hormones oestrogen and progesterone, and examine their influence on infectious diseases with particular reference to infections of the urogenital tracts. Females have been reported to have decreased cell mediated immunity (CMI) responses compared with males and numerous studies suggest that oestrogens can diminish CMI in both humans and rodents although this has been disputed by some investigators. T suppressor (CD8+) lymphocytes are capable of binding oestradiol, which may then be transported intracellularly to receptors in the cytosol or nucleus. Oestrogen receptors have not been identified on T helper (CD4+) lymphocytes or B cells, although there may be an indirect action upon antibody production and T helper cell function via the synthesis of interleukin 1 (IL-1) and interleukin 6 (IL-6). Oestrogen receptors have also been identified on lymphoid cells, thymic cells, and mononuclear cells in peripheral blood. Natural killer (NK) cell activity is reported to be lower in women than in men and may be decreased by the use of oral contraceptives and during pregnancy as oestrogen levels rise. Although physiological doses of oestrogens have no effect on NK activity in vitro, oestrogen treatment of cas-tressed and normal mice produces a significant decrease in NK activity in spleen and lymph nodes. One study has suggested that this oestrogen mediated decrease in murine NK activity may be due to the stimulation of T suppressor cells. Phagocyte function may be reduced in pregnancy and, specifically, by oestrogens, possibly secondary to altered lymphocyte function. Oestrogens may also enhance neutrophil migration and chemotaxis.

Non-specific factors also play an important role in protecting the genital tract from infection. Cervical mucus provides a barrier to potential pathogens by interfering with bacterial adherence and may, in addition, potentiate bacterial killing by phagocytic cells. In the human female genital tract, mucus production is clearly under hormonal control with dramatic changes in viscosity being reported during the menstrual cycle. Considering non-mucosal humoral responses, oestrogen increases immunoglobulin M (IgM) production in response to T dependent antigens, enhances immunoglobulin expression on plasma cells and T dependent B cell proliferation. The concentration of oestrogen used in many of these studies appears to be critical. For example, macrophage function, such as lysosomal enzyme activity, IL-1, and IL-6 secretion are increased by physiological doses of oestrogen, in contrast with supraphysiological doses which inhibit IL-1 production and superoxide anion generation. In addition, oestriol at physiological concentrations enhances the production of tumour necrosis factor α (TNFα) by peritoneal macrophages from rats. The hormonal regulation of mucosal immunity has been studied extensively by Charles Wira and his coworkers using animal models. The rat and murine oestrous cycle may be divided into three stages: pro-oestrus, just before ovulation and associated with rising oestrogen levels; oestrus, oestrogen dominated; dioestrus, pro-gestosterone dominated. Endocrine changes during the oestrous cycle regulate the levels of immunoglobulin A (IgA) and immunoglobulin G (IgG) in rat uterine and cervicovaginal secretions. Vaginal IgG levels decrease at the time of oestrus, a finding probably related to decreased transudation of serum IgG secondary to vaginal epithelial thickening which occurs at this stage of the cycle.
reported increase in the number of IgA plasma cells in mouse genital tissues during pro-oestrus and oestrus is likely to account for the rise in IgA levels at this time.\(^6\) In addition, there is an increased production of secretory component in the uterine epithelium that fluctuates during the oestrous cycle but which is associated with oestradiol administration.\(^{46-51}\)

Interestingly, since oestrus is the time of mating it has been suggested that the high levels of IgA present in the vagina during oestrus may serve a protective role against the increased pathogen load associated with coitus.\(^5\) Cyclical changes have been shown for secretory IgA and total immunoglobulin levels in vaginal secretions and endometrial tissue in humans.\(^{52-55}\); however, since our mating habits tend to be non-cyclical any protective effect against sexually transmitted pathogens may be of less relevance than for rodents. Antigen (Ag) presentation within the uterus and vagina is also partly hormonally controlled. Rat studies have demonstrated increased uterine cell Ag presentation at pro-oestrus, the stage of the reproductive cycle just before ovulation when oestradiol levels rise, compared with the time of ovulation, when Ag presentation is reduced.\(^5\) The same group has also shown that vaginal Ag presentation is inhibited by oestradiol but not by progesterone.\(^7\) As part of Ag presentation, foreign proteins are taken up by antigen presenting cells (APC), “digested”, and then presented on the cell surface in a membrane bound form with MHC class II molecules to Ag specific T lymphocytes.\(^{56,57}\) Although the number of MHC class II bearing cells increases in response to oestrogen in the rat uterus,\(^5\) this has not been demonstrated in human uterine tissue.\(^4\) Of more relevance to humans are the studies reporting interferon gamma (IFN-\(\gamma\)) receptors in human endometrial tissue\(^8\) and evidence for IFN-\(\gamma\) mRNA stimulation by oestradiol.\(^9\) IL-6 plays an important role in modulating mucosal antibody responses and it is now clear that oestradiol regulates IL-6 production.\(^{66-67}\) Both cytokines and sex hormones may be seen to play central roles in the regulation of mucosal immune responses in the female reproductive tract. Much of this knowledge arises from rat models and further studies are therefore required to determine the relevance of these findings to humans.

Having outlined some of the more important aspects of the interaction between sex hormones and genital tract mucosal immunity we will now consider specific genital tract infections and examine the role played by sex hormones in modulating their presentation and outcome in both animal models and humans.

**Gonorrhoea**

Clinical observation provided the first clues to the possible interaction between sex hormones and gonococcal infection. Gonococcal pelvic infection and disseminated gonococcal infection (DGI) are both more likely to occur at the time of menstruation.\(^{48-50}\) Oral contraceptive users have been reported to act as a risk factor for gonococcal infection,\(^{51,52}\) with the greatest risk being associated with formulations containing the more androgenic progestins.\(^{73}\) Animal studies have shown that female mice are most susceptible to gonococcal infection at the pro-oestrus stage.\(^{74}\)

The vaginal colonisation of germ free female mice requires prior treatment with oestradiol, whereas mice given progesterone or no treatment fail to colonise.\(^7\) In addition, further studies have shown that oestradiol treatment enhances mouse susceptibility to disseminated gonococcal infection possibly by adversely affecting the bactericidal activity of polymorphonuclear leucocytes (PMNL) mediated by myeloperoxidase.\(^{75}\) The ability of PMNL to release superoxide anion was not affected by oestradiol.\(^7\) The menstrual clustering of gonococcal pelvic infection may be partly related to an effect of human chorionic gonadotrophin (hCG) on the upper genital tract mucosal immune response, particularly with respect to gonococcal invasion of fallopian tube epithelium.\(^{76}\) hCG in high concentrations is capable of blocking gonococcal invasion of fallopian tube non-ciliated cells, whereas a marked increase in mucosal invasion is seen if hCG is removed from fallopian tube organ culture just before inoculation with gonococci.\(^7\) Additional factors which may influence upper genital tract invasion by gonococci include cervical mucus lactoferrin secretion and bacterial adherence. Lactoferrin is a glycoprotein present in most mucosal secretions which has been shown to inhibit the growth of bacteria requiring iron for normal metabolism in addition to having a direct bactericidal effect.\(^7\)\(^8\)\(^9\) Vaginal lactoferrin concentration varies dramatically during the menstrual cycle with the lowest levels being detected just before menstruation.\(^9\) Bacterial adherence to mucosal epithelial cells is an important determining factor for colonisation and subsequent infection and may be influenced by several factors, including sex hormones. *Neisseria gonorrhoeae* has been shown to adhere strongly to vaginal epithelial cells,\(^{81,82}\) with the degree of adherence varying according to the stage in the menstrual cycle.\(^5\)

**Chlamydial infection**

As with gonorrhoea, clinical studies have shown that chlamydial pelvic inflammatory disease more commonly presents just before or at the time of menstruation.\(^8\) Oral contraceptive users have been reported to show less marked antichlamydial activity of cervical secretions\(^8\) and, in keeping with this finding, a higher prevalence of cervical chlamydial infection compared with non-users.\(^3,5\) A recent meta-analysis of 29 case-control studies found an almost twofold increased risk of chlamydial infection for oral contraceptive users.\(^8\) Although these findings have been difficult to reconcile with the reports of a partially protective effect of oral hormonal contraception on pelvic infection,\(^8\) a recent study has shown that pelvic infection and DGI is more commonly seen in pregnant than non-pregnant women.\(^70\) In addition, oral contraception has been reported as a risk factor for gonococcal infection,\(^7,73\) with the greatest risk being associated with formulations containing the more androgenic progestins.\(^73\) Animal studies have shown that female mice are most susceptible to gonococcal infection at the pro-oestrus stage.\(^74\)

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Importantly, it has recently been shown that the stage of the menstrual cycle influences the ability to detect C trachomatis by enzyme immunoassay; infection being more commonly detected in women during the latter part of the cycle.99

In the laboratory, oestradiol has been reported to enhance the infection of HeLa cells by Chlamydia trachomatis90 and by the agent of guinea pig inclusion conjunctivitis (GPIC).91 Studies using McCoy cells have also demonstrated enhanced infection with C trachomatis after treatment with oestradiol, an effect inhibited by antioestrogens.92 Using a human endometrial epithelial cell system, Maslow et al found that the degree of chlamydial attachment was significantly and reproducibly increased when the endometrial gland epithelial cells were obtained from women in the early phase of the menstrual cycle and maintained in vitro by physiological doses of oestradiol.93 When epithelial cells were obtained from women in the later phases of the menstrual cycle and the explants were maintained in oestrone and progesterone, there was a significant reduction in chlamydial attachment. This effect correlated with the progesterone concentration. A number of studies have used the guinea pig model and shown that continuous treatment of ovariectomised guinea pigs with physiological levels of oestradiol increases the length of chlamydial infection.94 Similarly, treatment of guinea pigs with oestrogen dominant oral contraceptives increased the incidence of hydrosalpinx formation compared with control animals.95 Progesterone was found to have no effect on the course of the infection.96 More recently, Rank et al reported that the degree of upper genital tract damage (chronic inflammation and fibrosis in the mesosalpinx) produced by the intravaginal inoculation of GPIC was significantly related to the time in the oestrous cycle when the organisms were inoculated.97

In mice, C trachomatis infection is cycle dependent and the establishment of lower genital tract infection is enhanced by pretreatment with progesterone.97 98 Some workers have questioned the relevance of these studies to humans, in particular the use of the guinea pig and mouse models and strains of chlamydia other than C trachomatis.99 In the monkey, oral contraceptives have been recently found to have no effect on the course of chlamydial acute salpingitis in terms of length of recovery of C trachomatis and intensity of the inflammatory response in autotransplanted salpingeal tissues.90

Trichomoniasis
Trichomonad movement and attachment to cells appears to be affected by the presence of oestrogen90 and protein containing oestrogen binding sites have been identified in Trichomonas vaginalis and other trichomonads pathogenic in non-human species.101 102 However, studies examining the effect of oestrogens on the growth of T vaginalis using different incubation conditions have produced varying results. Thus oestrogens have been reported to decrease the infectivity of T vaginalis in vitro103 104 but increase infectivity in animal models.105 106 In addition, treatment with oestradiol enables T vaginalis to infect animals which are not natural hosts for the pathogen.107

Candidiasis
There is good clinical evidence that hormonal changes influence acute episodes of acute vulvovaginal candidiasis in some women. For example, there is an increased incidence of Candida albicans vaginitis in pregnant women, women taking high oestrogen oral contraceptives, and in women on post-menopausal oestrogen hormone replacement therapy.107 108 Oestrogens have been shown to increase vaginal epithelial avidity for C albicans109 110 and infection in rats is enhanced by oestrone.109 110 Oestradiol directly stimulates C albicans to switch from the yeast to the hyphal form111 and hyphal growth may pass through the cornified vaginal epithelium after treatment with oestrogens.109 110 The effect of oestrogens on C albicans may be partly explained by the presence of an oestrogen binding protein that displays high affinity for oestradiol and oestrone.112 A corticosteroid binding protein with high affinity for both corticosterone and progesterone has also been identified.113 114 Madani et al have proposed that the metabolic changes responsible for yeast to mycelial formation result from the inhibition of the enzyme NADPH oxidase (via allosteric modification) by oestradiol following binding with a flavoprotein receptor.115

Although less information is available on the role of progesterone, this hormone would appear to have an inhibitory role with respect to candidal pathogenicity, possibly via inhibition of monocyte function. Using peripheral blood lymphocyte cultures, candida specific lymphocyte proliferation was shown to be reduced by 50% in the presence of progesterone, an effect reversed by the removal of monocytes from the cultures.116 In addition, the anti-candida activity of polymorphonuclear leucocytes from naive as well as oestradiol treated mice is suppressed by the presence of progesterone.117 These findings are of some clinical importance as progesterone preparations have been used effectively to treat some women with recurrent episodes of vulvovaginal candidiasis.118 119

Bacterial vaginosis and vaginal infection with ureaplasmas and mycoplasmas
Furr and Taylor-Robinson have examined in detail the effect of sex hormones on the vaginal microflora in mice. Oestradiol induces cessation of the murine cycle at the oestrus stage and predisposes the animal to genital infection with Ureaplasma urealyticum120 121 and Mycoplasma hominis.122 123 Colonisation with U urealyticum persisted for up to 5 months and, in some animals, the organisms spread beyond the vagina to infect the ovaries and, occasionally, extragenital sites.124 Mycoplasma pulmonis, primarily a murine respiratory pathogen, is capable of colonising the vagina after treatment with progesterone, which arrests the reproductive cycle in the dioestrus stage.124 125 However,
the administration of oestradiol during the course of *M* *pneumonia* infection leads to the rapid elimination of organisms from the genital tract. This distinction between “oestrogen dependent” and “progesterone dependent” mycoplasmas is of some interest. Further studies have shown that mycoplasmas dependent on progesterone metabolise glucose and have strong haemadsorptive and other attachment properties. In contrast, oestrogen dependent mycoplasmas predominantly metabolise arginine or arginine/glucose and show less marked cytadsorptive properties. These observations suggest the presence of vaginal epithelial cell receptors which are under hormonal control.

As with most animal studies, the relevance of the findings to humans must be considered with caution; however, there are some interspecies similarities which deserve attention. Bacterial vaginosis (BV) serves as a useful example. Oestradiol treatment of mice leads to an increase in the number of endogenous vaginal bacteria, many of which adhere to vaginal epithelial cells, and a greatly reduced number of PMNL, a picture almost identical to that seen in BV. The multiplication of bacteria in “oestrogen induced oestrus” is greater than that seen in naturally occurring oestrous. Similar changes in bacterial flora have been recorded during the reproductive cycle of the rat. Further evidence for a possible hormonal role in the pathogenesis of BV comes from the studies showing changes in the human vaginal microflora during the menstrual cycle. For example, *Bacteroides* species, commonly found in high numbers in BV, are more prevalent in the first half of the menstrual cycle. In addition, some *Bacteroides* strains have been reported to use oestradiol or progesterone as growth factors. Studies examining the vaginal microflora in women after hormonal manipulation should provide useful information to help clarify the role of oestrogen and progesterone in the pathogenesis of BV and possibly other genital infections.

**Escherichia coli infection**

An association between oestrogen and urinary tract infection (UTI) in premenopausal women has recently been reported by Hooton et al. Women were significantly more likely to present with acute cystitis between 8 and 15 days after the onset of the last menstrual cycle than at any other time of the cycle. This association was true for women with UTI caused by *Escherichia coli* and *Staphylococcus saprophyticus*. In post-menopausal women, oestrogens appear to have a protective role against UTI. The vaginal colonisation by lactobacilli in premenopausal women is promoted by the presence of circulating oestrogens. Lactobacilli produce lactic acid from glycogen and maintain a low vaginal pH that inhibits the growth of many potential uropathogens.

The production of bactericidins may also play a protective role. In post-menopausal women, when oestrogen levels are low, vaginal lactobacilli decrease appreciably and are replaced by *Enterobacteriaceae*, especially *E. coli*. This is thought to account, at least in part, for the increased susceptibility to UTI after the menopause. Other potential predisposing factors associated with low levels of oestrogen include mucocutaneous androgen and decreased mucin secretion. The role of oestrogen deficiency is further highlighted by the studies showing that topical or orally administered oestrogens protect post-menopausal women from recurrent UTIs. In contrast, and in keeping with findings in premenopausal women, animal studies have shown that the establishment of urinary tract infection in animals is promoted by oestrogen treatment, with one study documenting decreased antibody coating of urinary tract bacteria despite high bacterial colony counts. Mucosal adherence is an important factor determining bacterial pathogenicity and there are a number of studies examining specifically the effect of oestrogens on *E. coli* adherence in the urogenital tract. In women, the adherence of *E. coli* varies through the menstrual cycle with peak adherence being noted in the early phase of the cycle and poorer adherence after ovulation. Oral contraceptive use has been shown to increase adherence of *E. coli* and oestrogen treatment of rats similarly increases adherence. More recently, the ability of vaginal mucus to bind *E. coli* expressing type 1 pili has been reported to vary through the menstrual cycle, although this appeared to be on a day to day basis and the specific effect of oestrogen and progesterone on binding was not assessed. Using a rat uterus model, Nishikawa and colleagues have shown that oestradiol reduces the binding of *E. coli* to endometrial cells.

**Human papillomavirus infection**

Clinical observation, animal studies, and in vitro studies suggest that HPV infection may be influenced by sex hormones. Several studies have indicated a higher risk of cervical neoplasia in users of oral contraception and in pregnant women. In addition, pregnancy appears to be associated with persistence of HPV infection. The precise mechanism(s) whereby oestrogen or progesterone contribute to HPV persistence or HPV associated neoplasia is obscure. The oncogenic transformation of baby rat kidney cells by HPV 16 is dependent on the presence of progesterone or norgestrel, a closely related derivative. In addition, the oncogenic transformation of baby mouse kidney cells has been reported using a combination of HPV 16 and ras oncogene in the presence of the closely related derivative of progesterone, R3020. Steroid responsive elements have been identified within the viral promoter region of HPV-16 and the 1 kb enhancer region of HPV-16. This has been shown to contain response elements for progesterone and glucocorticoids. Oestrogen...
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is also reported to transactivate the viral genome in HPV containing malignant cell lines.157 Although oestrogen may contribute to HPV persistence and neoplastic progression by increasing viral gene expression other studies have suggested that sex hormones and HPV oncogenes also cooperate at a different level to produce neoplastic transformation. For example, oestrogen has been shown to act directly as a carcinogen, possibly via products of oxidative metabolism.166 Moreover, HPV infection may increase the formation of these carcinogenic metabolism.168 Moreover, HPV infection may be a carcinogen, possibly via products of oxidative metabolism.168 In addition, chronic oestrogen administration causes persistent proliferation of cervical squamous epithelium170 and induces neoplastic change in female keratin 14 (K14) HPV 16 transgenic mice.171 Steroid receptors or related proteins have been identified in normal squamous cells of the female lower genital tract including the normal cervix,172–175 in CIN lesions,174 175 and in low levels in some cases of cervical cancer.176 Monsenego et al found borderline levels of oestrogen receptors and moderate levels of progesterone receptors in samples of normal cervix.154 Flat condylomata on squamous metaplasia, high grade CIN and underlying stromal cells expressed significantly higher levels of progesterone receptors than oestrogen receptors compared with normal cervix and genital warts. Others have reported decreasing levels of oestrogen receptors with increasing severity of CIN.175 Thus, under in vivo conditions, progesterone may act directly on HPV 16 and 18 genomes, especially within lesions of high grade CIN. Oral contraception appears not to alter hormonal receptivity in the normal cervix or CIN lesions177–179 and receptor levels remain relatively constant through the menstrual cycle.172–175

The interaction between sex hormones and anogenital HPV infection is undoubtedly complex with the above studies suggesting both a direct effect on HPV transcription via response elements in the viral long control regions and an indirect effect leading to increased levels of HPV oncogene expression.

Genital herpes simplex virus infection
Clinical observation suggests that sex hormones may influence certain aspects of genital herpes simplex virus (HSV) infection. In humans, recurrences may be triggered by menstruation179–182 and pregnancy has been reported to increase the frequency of recurrences in some women.179 183 Studies in mice also suggest a hormonal influence of pregnancy on HSV infection with pregnant animals proving more susceptible than non-pregnant mice to infection. In these experiments, susceptibility was determined by the frequency of animal death due to encephalitis following intravaginal inoculation of the virus. This observation in pregnant mice is thought to be related to levels of progesterone which rise early and remain elevated late into the pregnancy.184–186 Simulating pregnancy by administering progesterone to non-pregnant mice results in a high death rate following HSV inoculation185 and further studies have shown that mice require pretreatment with progesterone for a minimum of 3 days before an increased susceptibility to infection is observed.187 More recently, Teepe et al have shown that mice inoculated during dioestrus have a significantly higher death rate than mice inoculated at other times in the cycle.188 The authors suggest that this may be related to vaginal epithelial thinning, a raised vaginal pH, or an increased quantity of vaginal mucus seen at dioestrus.

Genital humoral immune responses in mice to intranasal immunisation against HSV type 2 have also recently been shown to be related to the oestrous cycle. Anti-glycoprotein B (anti-gB) specific IgA titres in vaginal washes were significantly higher during oestrus than dioestrus, whereas specific IgG titres were significantly higher during dioestrus than oestrus.52 This was further demonstrated in hormone treated mice where progesterone administration, which induces a dioestrous-like state, produced elevated specific IgG to IgA ratios. Interestingly, when specific IgG titres were at their highest levels, specific IgA titres were very low or undetectable. Unimmunised mice were only susceptible to intravaginal infection with HSV type 2 during dioestrus but not during oestrus. In addition, intranasally immunised mice given progesterone were protected from a lethal intravaginal challenge with virus, despite the fact that virus replication was present for 4 days after the challenge.52

Summary
In summary, this review has attempted to examine the potential role played by sex hormones, in particular oestrogen and progesterone, in the pathogenesis of urogenital tract infection. Many of the studies quoted relate to animal models and one must be cautious before extrapolating these findings to infection in humans. Nevertheless, there are now sufficient data to appreciate a hormonal influence on both humoral and cell mediated immunity and on non-specific factors such as bacterial

- Gonococcal and chlamydial infection is more common at the time of menstruation.
- Female mice are more susceptible to gonococcal infection at pro-oestrus (rising oestrogen levels).
- Oestrogens increase vaginal epithelial avidity for Candida albicans.
- Oestradiol directly stimulates C albicans to switch from the yeast to hyphal form.
- Oestradiol treatment of mice leads to an increase in the concentration of endogenous vaginal bacteria, a picture almost identical to that seen in bacterial vaginosis.
- Oestrogen may contribute to HPV persistence and dysplastic progression by increasing viral gene expression.
- In mice, progesterone may enhance pathogenicity of herpes simplex virus.
adherence. Possibly most importantly, immune regulation may be exerted locally at the level of the genital tract mucosa. In addition to an effect on local host defenses, sex hormones may directly influence micro-organism virulence. Women with recurrent urogenital infection are of particular interest, and although “infection induced immunosuppression” has been forwarded as an important factor, 18 the role of sex hormones has not been adequately assessed in these patients. The interaction between host and micro-organism is inevitably complex and the role played by sex hormones should be viewed as just one of many potentially important influential factors. The importance of urogenital infection as a cause of female morbidity together with the commonplace use of hormones both pre- and post-menopausally serves to highlight the need for further study into this particular aspect of disease pathogenesis.


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