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GYNECOLOGIC ISSUES IN THE HIV-INFECTED WOMAN

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Abstract

With the advent of highly active antiretroviral therapy (HAART), women living with HIV can now enjoy longer lifespans in relative good health as well as the prospect of bearing children with an overwhelmingly low risk of vertical transmission. Thus, increasingly, seropositive women are now facing issues around longevity as well as those associated with fertility. The clinician caring for the HIV-infected woman must be alert to the gynecologic issues that are prevalent in this population. Among those faced by the gynecologist are menstrual abnormalities, lower genital tract neoplasia, sexually transmitted infections, the need for gynecologic surgery, and menopausal issues including osteopenia/osteoporosis. Contraception in HIV seropositive women presents unique management issues, because of the necessity for a dual role of prevention of both pregnancy and HIV transmission, the possible effect of birth control on HIV infection, and the interaction between birth control and HIV therapies. With ever increasing frequency, the gynecologist will be presented with the seropositive woman or couple who wishes to conceive. The purpose of this chapter is to review the current knowledge on the relationship between HIV infection and menstrual abnormalities, genital neoplasias, contraceptive options, surgical complications, and menopause with its associated disorders. Special considerations in the seropositive woman contemplating pregnancy will also be discussed. The treatment of pelvic infections is discussed elsewhere in this volume, and only changes in standard therapy because of concurrent HIV-infection will be discussed here.

Menstrual Disorders

HIV infected women frequently report changes in their menstrual cycles (1), and early reports suggested an increase in abnormal menses in this population (2,3). HIV infected women may have menstrual dysfunction for a variety of reasons which are not directly related to their disease. In the United States, women infected with HIV are disproportionately poor and have an increased frequency of illicit drug use (4), which may cause amenorrhea. One study demonstrated that low socioeconomic class itself is associated with a higher frequency of amenorrhea (5). Co-morbid conditions such as psychiatric illness and the subsequent use of psychotropic drugs may cause amenorrhea as well. HIV-seropositive women are exposed to multiple stressors (6), a phenomenon known to cause amenorrhea by increasing levels of corticotropin-releasing factor, which subsequently reduces gonadotropin-releasing hormone (7). The thrombocytopenia that is sometimes associated with HIV infection (8,9), or with some antiretroviral therapy such as Indinavir (10) may be associated with menorrhagia or metrorrhagia. Menstrual abnormalities are common with associated conditions such as renal

insufficiency (11), and amenorrhea is often seen in conjunction with liver disease (12). A recent report of a 14-year-old girl started on HAART and followed with sequential ultrasounds demonstrated the development of polycystic ovaries onographically along with amenorrhea, acne and hirsutism 56 weeks after starting therapy (13). Lastly, severe weight loss from any cause, prevalent in one third of HIV-positive patients in one longitudinal study (14), can result in amenorrhea.

Although amenorrhea is a common result from many of the conditions associated with HIV infection, it is much harder to answer the question of whether or not HIV infection in the absence of severe disease or weight loss is associated with amenorrhea. Grinspoon (15) studied 31 HIV-infected women who retrospectively reported their menses. The prevalence of amenorrhea in this group was 20%, compared to the background rate of 5% in the general population (16). This rate went up to 38% in women who were at less than 90% ideal body weight, clearly demonstrating an association between wasting and amenorrhea. Amenorrhea was associated with a decrease in muscle mass and serum estradiol levels, and was noted in 17% of the women without wasting. Chirgwin studied 248 seropositive women without AIDS and matched them with 82 seronegative controls (16). A significant increase in amenorrhea was noted in the HIV-infected women compared with controls (5% and 0% respectively) when controlling for age, substance use, and race, yet the prevalence of amenorrhea in the seropositive women was equal to that reported in the normal population. On multivariate analysis, there was no association between amenorrhea and CD4 cell count or category B symptoms (17). Interestingly, a decrease in premenstrual symptoms among HIV infected women was reported, which was felt to be due to an increase in anovulatory cycles. Other studies show no association between HIV serostatus and amenorrhea (18,19). Among these is a large prospective study using menstrual diaries (20). In this study 802 seropositive and 273 seronegative women were compared while controlling for body mass index (BMI), substance use, and age. No difference in amenorrhea was found between HIV-seropositive and seronegative women, with a prevalence that was very low in both groups. There was a trend toward shorter cycles and more cycle variability among seropositive women with high viral loads and low CD4 cell counts. A study comparing women with CD4 cell counts between 200 and 500 cells/ μ l to women with CD4 cell counts under 100 cells/ μ l demonstrated a prevalence of amenorrhea of 9% and 19% respectively, illustrating an association between immunosuppression and amenorrhea, at least at the more severe end of the spectrum (21).

Because of a large body of literature on low testosterone levels and hypothalamic-pituitary dysfunction in HIV-infected men (22,23,24), parallel losses in ovarian function have been postulated in women. A decrease in testosterone levels has been demonstrated in HIV-positive women, even in the absence of wasting (15,25), and HIV infection is one of the known causes for the female androgen deficiency syndrome (26). Studies of ovulatory function in HIV-seropositive women have mixed results. While anovulatory cycles are reported to occur in 5–31% of healthy women with regular menses (27,28), they were reported in 48% of HIV-infected women in one small study, with a trend to occur more in women with low CD4 cell counts (29). Another small study reported anovulatory cycles in almost one third of HIV-positive women reporting normal menses (30), but a larger study of 55 HIV-infected and 10 negative controls reported ovulatory cycles in 96% of the seropositive and 78% of the seronegative women (31). At present it appears that HIV-positive women with regular menses do not have more anovulatory cycles than the general population, although good studies are lacking.

There is some literature to support HIV infection as a cause of premature ovarian failure. One study suggests an increase in serum FSH levels in seropositive women when compared to controls (25), and a study of 24 HIV-positive women aged 20–42 years reported a serum FSH level consistent with menopause in 8% (29). Menopause may be difficult to ascertain in this population because of amenorrhea secondary to wasting, and confusion between climacteric

symptoms and manifestations of coincident illness such as tuberculosis or side effects of drugs such as Efavirenz (10). In one study of 1130 seropositive and 292 HIV negative primarily African American women smokers, serum FSH was drawn and menstrual history was obtained every six months. Menopause was defined as amenorrhea for one year and a serum FSH of $>25\text{mIU/ml}$. The mean age of menopause was 47 years, regardless of serostatus, although the odds ratio of menopause if one was HIV seroinfected was 2.34(CI 0.63, 8.75). Over half of women with HIV and prolonged amenorrhea had a serum FSH in the premenopausal range (32), demonstrating that menopause is very difficult to ascertain in this group by the traditional WHO definition of amenorrhea for one year (WHO). This same group of women was asked if they were menopausal or not, and so were their clinicians. The women were more often correct about their menopausal status than their clinicians were (33). One study of women with a high prevalence of cocaine and heroin use and no confirmatory endocrine studies demonstrated a mean age of menopause (WHO definition) at age 43, with HIV infection and low CD4 count significantly associated with menopause (34). In contrast, a study in a similar population who were menstruating examined day 1–3 FSH, inhibin, and Mullerian Inhibiting Substance as markers of ovarian reserve. Levels were equal in seropositive and negative women controlling for age, supporting the notion that HIV infection does not affect ovarian reserve or cause ovarian failure (35). The effect, if any, of menopause on HIV infection is unknown, but a study of 382 HIV infected women with a known date of seroconversion compared CD4 counts between pre- and postmenopausal women. There was a trend toward lower CD4 counts in postmenopausal women (36). Menopausal HIV-infected women demonstrate a higher number of climacteric symptoms, most commonly psychological, vasomotor, and genitourinary symptoms (37,38).

In summary, although a significant proportion of HIV-infected women may be experiencing amenorrhea, HIV infection alone may not be responsible without coexisting conditions or with advanced degrees of immunosuppression or weight loss. The workup of amenorrhea in an HIV-infected woman should be similar to that in the general population. Serum FSH may be useful in making the diagnosis of menopause if this condition is suspected because of prolonged amenorrhea.

Lower genital tract neoplasias

The Centers for Disease Control and Prevention, in 1993, made invasive cervical cancer an AIDS-defining condition (17), and moderate and severe dysplasia were included on the list of conditions whose course or management may be complicated by HIV infection (category B conditions). These changes were made in response to the growing body of research in the early 1990's demonstrating that HIV-infected women have an increased prevalence of cervical dysplasia (39,40,41,42), although a similar association with cervical cancer has not been clearly proven (43,44). An association between cervical cancer precursors and immunosuppression in organ transplant patients has been known for some time (45,46,47), but the association in HIV-infected women is probably even greater. Seropositive women may have the shared risk factor of multiple sexual partners leading to an increase in Human Papilloma Virus (HPV) infection in addition to the immunosuppression associated with HIV infection.

The increased prevalence of squamous intraepithelial lesions (SILs) in HIV-infected women has been demonstrated repeatedly, in studies using cervical histology as well as cytology (43,48,49,50,51,52,53). A meta-analysis of 15 studies demonstrated an odds ratio of having cervical neoplasias of 8.8 for HIV-infected women, with the risk "likely increasing" with immunosuppression (54). Two large U.S. multicenter cohort studies, the Women's Interagency HIV Study (WIHS) and the HIV Epidemiology Research Study (HERS), have both demonstrated a prevalence of SILs on cytology in the 17–18% range for HIV-infected women and the 3–5% range for a seronegative control population with similar risk factors (50,55). The

seropositive women had an additional 18–21% prevalence of Atypical Squamous Cells of Unknown Significance (ASCUS) cytology, and, interestingly, they had an extremely low prevalence of high grade SILs and cancer, less than 3% in both cohorts. One small study of adolescents perinatally infected with HIV demonstrated a 47.5% incidence of abnormal cytology, including predominantly LSIL in this group (56). When serum retinol levels were assayed in 1314 women, an increase in SILs was associated with retinol deficiency (57). However, a review of the effect of retinoids on SILs concluded that they are well-tolerated but that they are not effective in causing regression of CIN 3 or preventing progression of any grade of CIN. They may, however, have some effect on regression of CIN 2 (58). In most studies the prevalence of abnormal cervical cytology and histology is associated independently with the degree of immunosuppression (40,41,43,59,60,61,62). In the HERS, HIV-infected women with a CD4 count ≥ 500 cells/ μ l had a prevalence of SIL equivalent to that in seronegative controls (55), and women whose CD4 counts were ≤ 100 cells/ μ l demonstrated a prevalence of low grade SILs and high grade SILs as high as 27% and 11% respectively (63).

It has been demonstrated in cohorts with a significant follow-up period that the increased risk of SILs persists over time, and the incidence of new histologically confirmed lesions was 20% in HIV-infected, and 5% in uninfected women in 3 years, with most of the increase in infected women coming from low grade SILs (64). Similar results were obtained cytologically in another cohort, and in both studies the incidence of high grade lesions remained low over time. The risk of incident SILs was dependent on HIV serostatus, HPV serostatus, CD4 cell count, and HIV RNA level (65). A recent study demonstrated an additional risk factor for SILs. They reported an increase in the detection of SILs among HIV seropositive and negative women who demonstrated cutaneous anergy when tested with *Candida*, tetanus, and mumps. Anergy is demonstrative of a decreased level of local cellular immune response (66).

In a large cohort study, progression to a more severe cytology in 6 months was demonstrated in 14% of the seropositive women and in only 7% of the HIV-negative women, and in a multivariate analysis only HPV serostatus and HIV-RNA were risk factors for progression. Regression without treatment in 6 months to a less severe cytology was common in both groups, however, occurring in 43% of HIV-positive and 66% of HIV-negative women. Regression, like progression, depended on HPV serostatus and HIV-RNA, but was also independently associated with CD4 cell counts. It is of note that neither progression nor regression was associated with HIV serostatus per se (65).

In an effort to understand the natural history of CIN 1 in women with HIV, 223 predominantly seropositive women and seronegative controls with CIN 1 were followed with serial cytology for a mean of 3.3 person-years. Progression occurred infrequently, and only in the seropositive women in the study. Regression occurred in 33% of the HIV-infected women, while the CIN 1 regressed in 67% of the controls. Regression was negatively associated with HPV and Latina race (67). Thus, in women living with HIV/AIDS most CIN 1 lesions will neither regress nor progress.

Although HAART may be expected to decrease SILs by restoring immune competence, it may conversely increase SILs by prolonging life and increasing the exposure time to HPV. Some studies show that there has not been a decrease in the incidence of cervical carcinoma since common use of HAART began (68,69), and only a small, non-significant increase in survival from cervical cancer has occurred in the HAART era as compared to previously (70). The effect of HAART on cervical and other malignancies remains incompletely understood (71). One small study of HIV-infected women with normal cytology at baseline demonstrated a non-significant decreased incidence of SILs in women on HAART when compared to untreated women (26.1% and 42.3% respectively) (72). Other uncontrolled studies show a high rate of regression of SILs in women after being placed on HAART (73,74). One prospective trial of

HIV-infected women with SILs at baseline demonstrated equivalent rates of progression and regression if taking no therapy, reverse transcriptase inhibitors, or HAART (75). Yet another large study demonstrated a significant increase in regression and decrease in progression with HAART (76). The effect of HAART on SILs is likely mediated through immune reconstitution, but some propose an additional direct antiviral effect of HAART on HPV (73,74). A more recent study demonstrates that although regression is dependent on HAART and the associated increase in CD4 count, most lesions in women on HAART do not regress (77).

HPV infection is the major cause of cervical dysplasia, and in HIV-negative women, it appears that most of the demographic and behavioral risks associated with SILs are entirely mediated through an increased prevalence of HPV (78). HPV is clearly associated with HIV infection, but this association has been difficult to elucidate. Several longitudinal studies of HPV infection have demonstrated that HIV-infected women are more likely than HIV-negative women to have cervical HPV of all types: low risk types (6,11,26,40,53,54,55,66,83,84), medium risk types (33,35,39,51,52,56,58,59,68,73,82), and high risk types (16,18,31,45), more likely to have persistence of cervical HPV over time, and more likely to have a high viral signal of their HPV. Moreover HPV persistence is associated with CD4 counts <200 cells/ μ l, and the presence of HPV is associated with an increase in progression and decrease in regression (55,65,79, 80). HPV is thought to be more associated with SILs than HIV infection alone. In fact, in women who are dually infected with HIV and HPV, SILs are felt to be 72.3% attributable to HPV infection and only 21.1% attributable to HIV infection in one analysis (55). Prevalence of any HPV type in the WIHS and HERS cohorts is approximately 65% in seropositive and 30% in seronegative women (55,65). When sera from women in these two cohorts were assayed for IgG to HPV-16 capsids, HIV-infected women were significantly more likely than HIV-negative women to have a positive HPV-16 serology, with a prevalence of 53–56%. Positive HPV-16 serology was strongly associated with the lifetime number of sex partners in all women. HIV-positive women had a prevalence of cervical HPV-16 by PCR of only 5–6%, suggesting that reactivation of HPV-16 is uncommon, and that HPV replication is controlled at the cervix even in immunocompromised women (81). A more recent study demonstrated that incident HPV infections occur even in women who are not sexually active, indicating that reactivation and/or autoinoculation of HPV can occur. This reactivation of HPV is very closely associated in seropositive women with CD4 count and viral load (82). Thus, pap smear screening is probably important in this population even if they are currently HPV negative and celibate.

It has been proposed that HIV and HPV interact in two ways: the immunosuppression caused by HIV may result in worse HPV infections, and the two viruses themselves may interact. That immunosuppression is important is supported by the fact that women with CD4 cell counts of ≥ 500 are not at an increased risk of SILs, and those on immunosuppressive therapy for organ transplants without HIV infection are at an increased risk of SILs as well. Various mechanisms by which the two viruses actually interact have been proposed. It was noted *in vitro* that the tat-1 regulatory protein of HIV increases expression and reverses suppression of HPV-16's regulatory gene (83). Cervical biopsies of HIV-positive women with SIL were compared to those of seronegative women who were matched for age, smoking status, and SIL grade for the mean count of Langerhans', or antigen-presenting cells. Seropositive women had significantly lower numbers of Langerhans' cells, and the number of cells was associated with CD4 cell count (84). A further analysis of cervical biopsy specimens revealed a decrease in macrophages among HIV-infected women (85), and others noted a unique CD8 lymphoid aggregate only in the biopsies of seropositive women with high grade SILs, suggesting impaired immunity at the level of the cervix (86).

A subject of debate in the past was how to best screen HIV-infected women for cervical dysplasia. Some authors have suggested that cytology is plagued with an increase in inadequate

specimens from inflammation in this group (87), and studies on immunosuppressed renal transplant recipients show high false-negative rates with cytology as well (88,89). In one small study, cytology and colposcopy were performed on 32 seropositive women, demonstrating cervical SILs in 41%, with only 7.7% of them detected cytologically (90). This alarming result led the author to recommend baseline colposcopy with subsequent twice yearly cytology for all HIV-infected women, but a decreased sensitivity of this magnitude was never duplicated elsewhere. Further studies indicate that cytology is an adequate screening tool in this population (43,91,92,93). One study suggests that cytology and colposcopic impression correlate poorly with final histology, but that the correlation is equivalent in seropositive and seronegative women (94). A small Italian study suggests that cytology, with a sensitivity/specificity of 89.7% and 75.0% in seropositive women is a more accurate diagnostic tool than colposcopic impression, with a sensitivity/specificity of 79.3% and 75.0%, in this population (95). The United States Public Health Service recommends that HIV-positive women receive two cytologic studies in the first year of diagnosis, and, if normal, proceed with yearly cervical cytology (96). Various regimens for the detection of SILs have been analyzed in terms of the cost per quality-adjusted life years (QALY) saved. The USPHS regimen results in an increase of 2.1 months life expectancy at \$14,800/QALY, while semiannual cytology yields only 0.21 additional months of life expectancy at an additional cost of \$12,800/QALY. An extreme regimen such as semiannual colposcopy would cost over \$375,000/QALY with a minimal increase in life expectancy over the other regimens (97). A similar analysis of QALY subsequently demonstrated that if HPV testing were added to the initial cytologic screening with a modification of subsequent screens based on the results of the HPV assay, more cost effective strategies would ensue (98), as has been demonstrated in the past in the general population (99). Although some recommend routine anal cytology in HIV-infected women, this is not currently recommended (100,101,102). A study following HIV seropositive women who had normal pap smears and were HPV negative at baseline for 2 years demonstrated no high grade SILs at 2 years regardless of degree of immunosuppression, and an incidence of low grade SILs similar to that of HIV seronegative women if the CD4 count was above 500/microL. Thus one may argue that in this group of immunocompetent women who are HPV negative screening may be performed as in the general population (103). Currently, however, such screening practices in women living with HIV have not been adequately tested.

The diagnosis of SILs in HIV-infected women involves colposcopic-directed biopsies. These women should have colposcopy even after a single cytologic specimen showing atypia or low grade lesions. Several studies suggest that colposcopy is less predictive in this group than in the general population. One analysis of women with high grade lesions on a cone biopsy specimen revealed that 47% of the seropositive women had only low grade lesions on colposcopic biopsy. This is in comparison with 9% of the seronegative control group (104). Thus it seems wise to biopsy abnormal findings liberally. Because of the higher prevalence of vulvar, vaginal, and anal intraepithelial neoplasias in HIV infected women (87,92,93), careful attention should be paid to these sites during the gynecologic exam, with colposcopy and/or biopsy of any abnormalities.

Because of the possible decreased sensitivity of colposcopy, treatment should probably be excisional instead of ablative in this population (105). Some authors have suggested an increase in complications of treatment, such as bleeding and infection (105), but there is not adequate data to support this in the literature. In one study no women who had a hysterectomy for carcinoma in situ of the cervix had complications (106). A study of cryotherapy for low grade cervical lesions demonstrated a 1% recurrence in seronegative women, and a 48% recurrence in HIV-seropositive women (107), and perhaps alternate forms of therapy should be chosen. Any management other than observation for a low grade lesion on the ectocervix is a subject of debate, and should probably be reserved for patients with severe immunocompromise if done at all. As previously mentioned, cytologic regression has been reported in a substantial

portion of HIV infected women (65). In the Aids Clinical Trial Group (ACTG) 293, HIV-positive women with histologically proven low grade lesions were randomized to observation or isotretenoic acid by mouth, 0.5mg/kg/day for 6 months. Regression rates were high and progression rates were low in both groups, with similar findings in the two groups after 6 months, suggesting that observation alone is appropriate for most seropositive women with low grade lesions (108). In planning treatment, it is important to keep in mind the low rate of adherence with follow-up, reported as high as 35–63% in this population (106,109). Although recurrence rates are higher for seropositive women (107,110,111,112), treatment of high grade lesions is similar to that in the general population. A study of 45 HIV-positive women with cervical carcinoma in situ demonstrated a high rate of recurrence, 65% by cytology alone, after either cone biopsy or hysterectomy for treatment (106). One study following women after treatment for CIN demonstrated a treatment failure in 45%, with risks for failure being a CD4 count under 200 and being HPV positive after treatment. Recurrences were common in this study as well, although they were predominantly low grade (113). In ACTG 200 HIV-positive women were randomized after excisional treatment for high grade cervical lesions to observation or 5-FU cream applied vaginally. There were less high grade recurrences and a longer time until recurrence in the 5-FU group, although even in the treatment group the rate was high, 28% (114). This remains an alternative to repeat excisional therapy in the treatment of women with recurrent disease.

Contraception

In the HIV-seropositive woman, contraception must play the dual role of birth control and prevention of transmission of HIV and other sexually transmitted infections. The clinician must carefully consider if a contraceptive option is effective, will prevent HIV transmission, will interact with other medications the patient is taking, or will affect the HIV infection itself. Although there is a high correlation between HIV-RNA levels in the blood and HIV in cervico-vaginal secretions, the infected woman must understand that 20–35% of women with undetectable virus in their blood are positive for HIV in their cervico-vaginal lavages, and that she is capable of transmitting the infection even with undetectable viral loads (115,116).

One longitudinal study of HIV-infected women and seronegative controls found that consistent use of barrier methods was only seen in about one third of women, use of a barrier with an additional form of contraception was rare, and condom use was not even associated with HIV serostatus (117). In contrast, a cross-sectional study of seropositive women demonstrated that two thirds had used condoms consistently in the previous one month (118). Both studies involved primarily African American women.

As in the general population, condoms alone do not provide excellent pregnancy prevention, with a first year failure rate of 12% and a perfect use failure rate of 3% (119). They function well at transmission prevention, however. In vitro, they prevent passage of the HIV-virus, and in a large metaanalysis, condoms use resulted in a 69% decrease in transmission (120). A study of HIV discordant heterosexual couples demonstrated, through analysis of vaginal sperm, sexually transmitted pregnancies, pregnancy, and DNA sequencing of new HIV infections, that there was significant underreporting of sex without condoms (121). The European study group, however, followed a cohort of 123 serodiscordant heterosexual couples, in which either the male or the female were infected, for 22 months. In couples reporting inconsistent condom use there were 4.8 seroconversions per 100 person years, while in those reporting consistent use there were no seroconversions (122). Male-to-female transmission generally occurs much more frequently, except in Africa and other developing nations, where transmission rates are nearly equivalent (123). With the great potential for condoms to prevent transmission, it is important to know which groups of women are at increased risk for poor condom use, and counsel them appropriately. A study of 2864 women “at risk” for HIV infection demonstrated

as risk factors for poor use exchanging sex for money or drugs, binge drinking, having limited resources, and being dependent on one's partner (124). A study of women who had a tubal ligation demonstrated an extremely poor rate of condom use in this population, with only one-fifth as many using condoms as demonstrated in unsterilized women (125).

Seroconcordant HIV-positive couples should be advised to use condoms as well, both for prevention of other sexually transmitted infections and to prevent reinoculation with the same, or superinfection with a different strain of HIV. A study of such couples, however, shows a marked decrease in condom use when both members are HIV-infected. There was no increase in progression to AIDS or decreased survival in such couples who denied any condom use in some studies (126,127), but more recent data suggests the opposite is true (128). Although condom use does not prevent genital HPV infection, a recent meta-analysis demonstrated that their use may result in a decrease in condyloma or high grade cervical disease (129).

The female condom has been tested *in vitro*, and prevents HIV transmission in the laboratory (130). There are many errors in its use, however, with a 26% first year failure rate, usually due to ring slippage (131). The female condom protects more of the vaginal epithelium from exposure to semen, with a 3% probability of exposure as opposed to an 11% with the male condom (132).

In vitro, spermicides like nonoxynol-9 inactivate HIV within 60 seconds, but *in vivo* it does not appear to decrease the concentration of HIV in genital secretions. In a study of 6 rhesus monkeys, spermicides decreased seroconversion (133), but human studies are conflicting. A study of female sex workers in Kenya demonstrated an increased HIV acquisition with spermicide and sponge use together, probably secondary to inflammation and ulcers caused by such frequent use of spermicides in this population (134), making the CDC hesitant to recommend spermicide use for HIV prevention. One reanalysis of an observational study suggests that spermicides indeed prevent transmission (135), but a metaanalysis of multiple trials yields conflicting results, with a protective effect in one observational study and a nonsignificantly increased risk in one clinical trial (136). Seroinfected women with discordant partners should not use spermicides because of the potential for increased transmission to their partners (132). Newer spermicides which cause less inflammation are being tested to potentially decrease the risk of HIV transmission. Phase 1 and 2 studies of a substance with *in vitro* prevention of HIV transmission called PC 213, with iota-carrageenan, show little colposcopic evidence of inflammation or ulcers with its use (137), making it potentially promising.

Primate studies demonstrate that HIV-transmission can occur transvaginally without a cervix after hysterectomy, and a case was reported of a woman with cervical agenesis who acquired HIV sexually through a neovagina (138), demonstrating that coverage of the cervix alone would not be adequate to prevent transmission. Women using the diaphragm, sponge, or cervical cap need to know that these forms of contraception do not prevent transmission or acquisition.

Permanent sterilization is the chosen contraceptive method for many HIV-serodiscordant or concordant couples. Tubal ligation is clearly associated with a decrease in condom use, with one study demonstrating that over half of women who are sterilized have no plan to continue condom use (139), and this has been demonstrated in women living with HIV as well (140). Among seropositive men who went for vasectomy, a small subset had a resultant decrease in seropositive semen after the procedure, although this does not reliably occur (141). The use of sterilization among post partum women living with HIV has significantly decreased since the advent of the PACTG-076 trial (142).

Theoretically, the increase in duration and flow of menses associated with a copper containing intrauterine device (IUD) use could lead to an increase in transmission to partners. In the

European study group, however, there were no female-to-male transmissions in IUD users (143), and in a study of 98 seropositive IUD users, there was no difference in prevalence of cervical shedding of HIV before and 4 months after IUD placement (144). Similarly, the IUD theoretically could have a decreased efficacy in women with impaired immune systems, and is associated with anemia and an increase in pelvic infections. For these reasons, a World Health Organization expert group had decided in 2000 that IUDs were not appropriate for HIV-infected women (145). There is now an abundance of data suggesting the safety of IUDs in this population. An initial study was done in Kenya of over 600 women without active pelvic infections and not at high risk of such infections who were given IUDs and followed for 4 months. At all CD4 counts, the HIV seropositive women had no increase in overall complications (7.6% in seropositive, 7.9% in seronegative women), nor an increase in infectious complications (1.4% in seropositive, 0.2% in seronegative women), suggesting that IUD use is safe in carefully selected populations of HIV-positive women (146). A subsequent study of 12 seropositive women given the levonorgestrel-releasing intrauterine system demonstrated the following with its use: a decrease in menstrual bleeding, no ovulations, an increase in serum hemoglobin and ferritin, no change in CD4 or HIV-RNA levels, and no change in cervical shedding of the virus (147). The decrease in menstrual flow and lack of an effect on cervical shedding make the levonorgestrel intrauterine system especially attractive for women with seronegative partners. A recent trial in which 599 postpartum women were randomized to either a copper-containing IUD or hormonal contraception demonstrated decreased pregnancy rates and a decrease in disease progression with the IUD. There was one case of pelvic inflammatory disease in the IUD-using group (148). The World Health Organization changed their position in 2004, stating that the IUD may be initiated in HIV infected women without AIDS and in those with AIDS who are well on therapy, and that it may be continued, but not initiated in women with AIDS who are not on therapy (149). Women should be at low risk for and screened for sexually transmitted infections prior to IUD insertion, and the levonorgestrel-releasing system is an excellent choice of IUD in this population when available.

There is concern that oral contraceptive pills (OCPs) may be associated with an increase in HIV transmission. In theory, OCPs are associated with cervical ectopy, and ectopy may be associated with an increase in viral shedding and transmission. There are competing factors that may decrease transmission, however, such as the decreased bleeding and the increased cervical mucous viscosity associated with OCPs. The resultant decrease in vaginal pH seen in OCP users may, on the contrary, increase HIV transmission. A meta-analysis of the data suggests that no inferences can be made on an association between OCP use and HIV transmission (150), except, of course, through the well-known reciprocal association between OCPs and condom use. This association holds true among HIV-infected women as well, with less than half of infected women who are on OCPs reporting concurrent use of condoms (140).

Because of the plethora of effects that female hormones have on the immune system (151), there has always been concern that OCPs may affect HIV-infection. OCPs affect not only cell-mediated immunity, but natural killer cell, IgG, and IgM activity as well (151). Conflicting data about an effect of female hormones on HIV infection exist. Some animal models demonstrate hormonal regulation of retroviruses at the level of gene transcription (152). A primate study demonstrated an increase in HIV transmission and rapid progression in ovariectomized monkeys that had subcutaneous progesterone implants when compared to those with placebo implants (153), suggesting a harmful effect of progesterone. Data collected over the menstrual cycle, however, reveal a decreased viral load in women during the luteal phase of their cycle when progesterone levels are high (154). Similar concerns exist about other forms of hormonal contraception, with the added concern regarding transmission in depo-medroxyprogesterone acetate users because of an increase in vaginal bleeding. A longitudinal

study of seropositive women found no change in viral load and a statistically significant but clinically unimportant increase in CD4 count with hormonal contraception use (155). These women were using either contraceptive pills or progestin-only forms such as the depo-provera injection of subcutaneous levonorgestrel implants. Certainly there is abundant data on pregnancy in HIV-positive women to suggest that hormone use will not affect disease progression (156,157,158,159). Similarly, a recent study of over 300 women on combined oral contraceptive pills or depo-provera injections demonstrated no change in CD4 or HIV-RNA over the subsequent 24 months (160).

Hormonal contraceptive users must be aware of the possible interaction between hormones and many of the drugs used by HIV-positive women by way of the cytochrome p450 CYP 3A4 system (161). Various antiretroviral medications may act as cytochrome p450 substrates, activators, inhibitors, or, as ritonavir, nelfinavir, and efavirenz do, act as a combination of all three (162). The activation of this enzymatic system by the drug may decrease the concentration of steroid hormones, resulting in a decrease in contraceptive efficacy. This association has long been known for the antituberculosis drug Rifampin (163), but has now been demonstrated for several antiretroviral therapies as well, both non-nucleoside reverse transcriptase inhibitors and protease inhibitors. These studies are usually pharmacokinetic studies of healthy patients getting short term treatment with a single antiretroviral medication, and how applicable they are to long term use of multiple medications in a chronically infected woman is questionable (164). Data on 33 healthy female volunteers who were given Ritonavir demonstrates a subsequent decrease in the concentration of ethinyl estradiol (165). A pharmacokinetic study of 10 women on OCPs in which ethinyl estradiol and norethindrone levels were measured before and 30 days after Nevirapine use demonstrated a significant decrease in the concentration of both hormones after Nevirapine (166). A retrospective review of a database of 2053 women demonstrated OCP failure significantly more often in women with concomitant use of nelfinavir (167). Current recommendations for women using hormonal contraception concurrently with efavirenz or nevirapine are to use additional or alternative contraception (168). Certainly women on these antiretrovirals desiring oral contraceptives should be on a pill with at least 30 micrograms of estrogen and be counseled not to miss any pills.

A study looking at changes in depo-provera with use of nelfinavir, nevirapine, or efavirenz demonstrated no effect of these antiretrovirals on the concentration of the hormone (169). The same is probably true for levonorgestrel subcutaneous implants. Women on antiretrovirals using depo-provera, however, should be cautioned against getting subsequent doses beyond the recommended twelve weeks. After initiation of HAART, women using hormonal contraception responded similarly to non-users of hormones in terms of CD4 cell count and HIV RNA. These hormones, therefore, are probably not significantly decreasing the concentration of antiretrovirals in any clinically significant way (170). Deciding on a contraceptive method is difficult due to the many factors that need to be taken into consideration in the HIV-infected woman.

Surgical complications

Women with HIV may be at risk for an increase in gynecologic surgery for a number of reasons. One longitudinal cohort study reported that women living with HIV are more likely than seronegative controls to have a hysterectomy, and that this was most often done for cervical neoplasia (171). Other studies demonstrated a trend toward more tuboovarian abscesses, which often require surgical intervention, among women with pelvic inflammatory disease who were HIV infected (172,173). There is a paucity of literature about the rate of complications after gynecologic surgery in HIV infected women, but this can be extrapolated from the obstetrical cesarean section and other surgical data. The European HIV in Obstetrics group reported a post-cesarean section (elective and non-elective) complication rate of 42.7%, mostly from

febrile morbidity and anemia requiring transfusion (174). Seropositive and age, gender, and surgery matched negative controls were compared in a study of postoperative complications. The surgeries included gynecologic as well as other types of non-obstetrical surgery. The postoperative complication rate was similar in the two groups except for an increase in pneumonia and mortality at one year in the seropositive group. Complication rate increased as HIV-RNA went above 30,000 copies/ml, but CD4 count did not affect it. The group was quite healthy and the majority were on antiretroviral therapy, and febrile morbidity and the need for transfusion were not examined (175). Overall, in the seropositive patient having surgery one can expect a small increase in usually minor complications. This rate may be further increased in patients with a high viral load.

Osteopenia and osteoporosis

Because of the improved prognosis, and because 10–5% of new HIV infections in the U.S. are currently in people over 50 years of age, the population of seropositive people is aging. Disorders of bone mineral density appear to be more frequently seen in people living with HIV, and so the clinician caring for seropositive women needs to pay special attention to assessing and modifying their patients' risk factors for osteoporosis as well as screening for and treating it.

Initially the decrease in bone density was felt to be solely secondary to HAART, especially the protease inhibitors (176). In vitro studies have, in fact, demonstrated an increase in osteoclastic action with zidovudine (177) as well as impaired bone mineralization with the addition of tenofovir (178). More recent reports, however, have demonstrated an increase in osteoporosis and osteopenia in people who are infected but antiretroviral naïve (179,180,181), although in increase risk of fracture has never been demonstrated (182). A recent case report of a 6 year old antiretroviral-naïve HIV positive child with severe osteoporosis and multiple fractures supports a direct effect of the HIV virus on bone metabolism (183). Possible mechanisms of action include a direct effect of the virus on osteoclasts, chronic inflammation causing cytokine activation and an increase in bone absorption, or an alteration in the metabolism of vitamin D (183,184). Certainly comorbid conditions such as smoking, wasting or being bedridden may contribute to decreases in bone mineral density.

In an attempt to quantify the risk of osteoporosis attributable to HIV infection, Brown et al performed a meta-analysis and concluded that people who are HIV infected have a threefold increase of osteoporosis compared to seronegative controls (185). Those on antiretroviral therapy have a 2.4 fold increase compared to antiretroviral-naïve controls, and those specifically on protease inhibitors (PIs) have a 1.6 fold increase compared to non-PI treated controls. It is unclear, however, whether those on antiretrovirals are just a group who has been infected for longer, are older, and have more severe disease. Risk factors for low bone mineral density among seropositive individuals include low BMI, advanced age, female gender, high viral load, advanced stage of disease (186), low muscle mass, low testosterone level (187), and duration of illness (188).

Several studies have demonstrated that the bisphosphonate alendronate along with calcium and vitamin D is effective as well as safe for increasing bone mineral density in seropositive men and, although fractures were not significantly decreased, women (189,190,191,192). Treatment is usually taken once weekly

Screening guidelines for disorders of bone mineral density in HIV infected women have not been established. Since ACOG advises the screening of women with other risk factors at menopause (193), it makes sense to screen all seropositive women at menopause. Women with other risk factors or a long history of HIV infection may benefit from screening in the perimenopausal period or earlier.

Fertility

As the population of HIV infected individuals in this country has shifted from primarily gay and bisexual men to heterosexuals of childbearing age, the number of seropositive women contemplating pregnancy has drastically increased. Referrals to gynecologists caring for HIV infected women are sometimes made by infectious disease specialists caring for men who, with their partners, plan to start a family. In a survey of 2864 HIV seropositive adults, almost one third expressed a desire to have children in the future (194), and this number is consistent with that found in a study of 118 seropositive women. In this latter study, the desire for children was associated with young age, high CD4 counts, a newer relationship, and not being on antiretroviral therapy (195). Among women who had been sterilized, 12% expressed tubal regret.

Whether or not infertility rates are higher among HIV seropositive couples is a matter of some dispute. Infected women who have advanced disease (21) or are wasted (15) have an increase in anovulatory cycles. One small study demonstrated a 27.8% incidence of tubal occlusion on hysterosalpingogram among seropositive women (196), but this is not supported elsewhere in the literature. One would expect an increase in tubal factor infertility with HIV infection similar to what has been seen in other groups of women with sexually transmitted infections. Among seropositive males, increases in abnormal semen, including decreases in sperm counts, as well as normal sperm morphology and motility have been demonstrated (197,198). Thus, one can expect significant numbers of HIV-infected couples to seek assistance with reproduction because of infertility. It is the responsibility of the clinician caring for a seropositive woman contemplating pregnancy to discuss all of the following points: the risk of vertical transmission, the need to be on HAART during the pregnancy, the avoidance of drugs such as efavirenz during organogenesis, the role of cesarean section to decrease vertical transmission, and the importance of neonatal zidovudine.

Another reason such couples may pursue assisted reproduction is to decrease the risk of horizontal HIV transmission. In the serodiscordant couple with an HIV infected woman, this is easily affected through insemination with the partner's semen. Couples with limited resources may even elect to place semen in the vagina on their own.

The serodiscordant couple with an HIV positive male hoping to limit horizontal transmission is more challenging, and they will frequently present to the gynecologist for advice. Clearly adoption and insemination with donor sperm are the only options with no risk of transmission. A small study of 50 such couples seeking assisted reproductive techniques demonstrates that these options are not acceptable for many. If given no other options, 12% stated that they would resort to timed intercourse to conceive, and over half would not consider the use of donor sperm (199).

The serodiscordant couple contemplating timed intercourse should be counseled against this, as transmission occurs in 1 of 500 to 1 of 1000 instances of unsafe sex, with a 4.3% horizontal transmission rate reported in couples using timed intercourse to conceive (200). If they do proceed with timed intercourse, they should be counseled not to start until the male's viral load is undetectable, to avoid sexual contact if either partner has any other untreated sexual infections, ulcers, or bleeding, and to use ovulation predictors to accurately time their sexual contacts. They should confirm pregnancy before having unsafe sex in the next cycle so that they do not become infected during pregnancy. They should be aware that an undetectable viral load in plasma does not mean that there is no virus in the semen (201). One small Swiss study of 21 serodiscordant male positive couples demonstrated pregnancy rates of more than 70% with timed intercourse. In this study all males had undetectable viral loads in their plasma and semen. The women were given pre-exposure prophylaxis with tenofovir 12 and 36 hours before

intercourse. There were no HIV seroconversions at 3 months (202). Because of its rapid uptake, one tablet two hours before intercourse has also been recommended (203). Other investigators have proposed using vaginal estriol gel on days 1–5 to thicken the epithelium and potentially decrease horizontal transmission, although this has only been demonstrated in simian models (204).

Although there is a paucity of centers in the United States offering HIV infected males sperm washing for intrauterine insemination of HIV negative women, this has been done for 15 years in Europe (205). After case reports of unscreened donor intrauterine insemination (206) and insemination from washed sperm of an HIV infected husband (207) in the literature, the Centers for Disease Control in 1990 recommended against the insemination of semen from HIV-infected men. Nevertheless, over 4500 inseminations have been performed worldwide with no horizontal transmissions reported (203). Although it is well documented that the HIV virus is present in semen even in men with undetectable plasma viral loads (208,209), there is no evidence that it can be carried by sperm (210). Typically for these procedures semen is processed through gradient centrifugation followed by a swim-up procedure (205). Because HIV may be attached to sperm, and because HIV-associated proviral DNA may be present in seminal cells of men with undetectable viral loads (211), some researchers advocate testing the washed sperm for HIV-RNA (212) and even for proviral DNA (213) prior to its use. Kato recently published a technique he used for washing 73 semen samples with no proviral DNA or HIV-RNA detected using PCR with a detection limit of one copy (213).

Some researchers feel that the risk of exposure to millions of sperm as well as to other cellular debris associated with IUI is unwarranted in the face of in vitro fertilization- intracytoplasmic sperm injection (IVF-ICSI), which limits exposure to less than 20 sperm. Over 200 cycles of ICSI have been performed to date with no seroconversions (210), and a recent study comparing ICSI in 30 serodiscordant male positive couples and 79 HIV negative controls with tubal factor infertility demonstrated equal success rates regardless of serostatus (212). Others, however, believe that in light of the IUI safety record reported in the literature, the extra risk of ovarian hyperstimulation and multiple gestation seen with ICSI is not justified without male factor infertility as an additional indication for its use (215). There are very few centers that provide either service to HIV infected couples in the United States (210).

There is very little data on which to base recommendations to the HIV positive seroconcordant couple. Seroconcordant positive couples are typically counseled to practice safe sex, and superinfection with a different HIV strain has been demonstrated as a result of unsafe practices, with a subsequent worsening in the severity of infection (128). Such couples typically become pregnant without the aid of assisted reproductive technology, but it should be offered in order to possibly decrease the risk of superinfection (216).

Access to assisted reproductive technology, either for infertility or to limit horizontal transmission, remains limited in the United States. The Center for Disease Control's 1990 recommendation against artificial insemination as well as the American Society for Reproductive Medicine's 1994 guidelines expressing concern about horizontal and vertical transmission as well as the birth of a child to parents with a limited life span led practitioners away from helping infected couples become pregnant. The fact that inseminating a woman with HIV-infected semen constitutes a criminal offense in some states (216) has furthered such sentiments. The fear of nosocomial transmission of HIV to stored embryos and the need and cost for separate storage containers for seropositive gametes has also deterred infertility practices from including seropositive couples. Such cross-contamination in storage tanks with viruses has been demonstrated (217). A survey of assisted reproduction clinic managers reveals that only 6.5% of them feel that their services should be offered to seropositive women (218).

With the prolonged life span and low risk of vertical transmission that have gone hand in hand with the use of HAART, coupled with the frequent decision of seropositive couples to conceive, it has become incumbent upon the practitioner to counsel and assist such couples on the safest ways to proceed. The Ethics Committee of the ASRM published new guidelines in 2004 for the treatment of HIV infected individuals/couples concluding that HIV infection is considered a disability protected under the Americans with Disabilities Act, and that denying medical services because of HIV infection may be a violation of law (219).

Sexually Transmitted Infections

The treatment of most sexually transmitted infections is similar in HIV-infected and non-infected women (220). Only differences in treatment will be discussed here.

Herpes simplex virus-2 infections affect 50–90% of HIV infected individuals worldwide (221). The Centers for Disease Control in 1993 added a herpetic lesion present for at least one month's duration to the list of AIDS-defining illnesses (17). HIV-infected women tend to have more herpes simplex virus (HSV) infections of increased severity, with an increased healing time, and often an atypical presentation. They also have more frequent episodes of shedding of HSV-2 (222). HSV infections are more likely to be acyclovir-resistant in HIV-infected individuals, with a resistance rate of 5% (223) as opposed to 1% in the general population (224). The treatment of HSV infections in HIV-infected patients is the same as in non-infected patients for episodic infections, and is only slightly modified to include higher doses for recurrent or suppressive therapy. Long term use of acyclovir as suppressive therapy for up to 10 years in HIV-infected individuals is both effective and safe (223), and demonstrates no significant interactions with antiretrovirals (225). If a herpetic lesion persists in an HIV-infected patient on antiviral therapy, HSV resistance should be suspected and appropriate testing should be performed. Since acyclovir-resistant strains are usually not susceptible to valacyclovir or famciclovir, intravenous foscarnet should be used for treatment (221). HAART has been shown to reduce the incidence of herpetic ulcers, but it may not affect asymptomatic viral shedding (225). Because HSV-2 coinfection increases the chance of HIV transmission to seronegative partners, and because HSV-2 reactivation causes an elevation in HIV-RNA, there is some data to support serologic testing for HSV-2 in asymptomatic HIV-infected women, with chronic suppressive therapy in those demonstrating HSV-2 antibodies (225).

The prevalence of syphilis is increased among HIV-infected women, and neurosyphilis is more common in this population. Moreover, as an ulcerative disease, it facilitates HIV transmission to uninfected individuals. A mathematical model of HIV transmission was used to conclude that in the United States in the year 2000, approximately 545 new cases of HIV infection in African Americans were attributable to syphilis (226). Two studies examined the risk of treatment failure in seropositive individuals with syphilis. A British study reported equal failure rates in seropositive and negative patients (226), but a U.S. study reported significantly more failures among seropositive individuals (17% vs 5%) (228). In both studies a variety of treatments were used. One study of seropositive patients with syphilis who had a lumbar puncture done demonstrated an increase in neurosyphilis in women, in those with neurologic manifestations, and in those with a titer of greater than or equal to 1/32, suggesting that lumbar puncture need not be done in the absence of symptoms and with a lower titer (229). Treatment of syphilis in HIV-infected individuals is similar to that in the general population with the following exceptions: individuals should have an examination of their cerebrospinal fluid (CSF) performed prior to therapy if they have late latent syphilis or syphilis of unknown duration, or after therapy if there is a four-fold rise in non-treponemal titers during treatment or there is not a four-fold decrease by 12–24 months after treatment. Ceftriaxone and azithromycin should not be used for treatment in patients with HIV infection (230). Penicillin-allergic individuals should be desensitized and treated with penicillin. In addition, some, but

not most, experts recommend treating primary and secondary syphilis with the 3 weekly injections of penicillin usually reserved for latent syphilis, and some recommend an examination of the CSF even in early syphilis (220). Dual-infected individuals should have RPR titers followed for 24 months with late and 12 months with early disease as they can take longer to fall (230).

HIV-infected patients who have chancroid are more likely to have treatment failure and to require longer courses of therapy. Some specialists recommend not using the single-dose options for treating these patients, especially if follow-up cannot be ensured (220).

Early reports of pelvic inflammatory disease in HIV-infected women suggest that presentation may be atypical in this population, with an increased need for surgical interventions and an increase mortality rate (231,232,233,234). In 1993, pelvic inflammatory disease, “especially with a tuboovarian abscess” was even included in the list of Category B symptoms (17). More recent data suggest fewer differences in pelvic inflammatory disease between seropositive women and the general population, with HIV-positive women more likely to have tuboovarian abscesses, but responding well to outpatient treatment (235,236,237). Studies have demonstrated more prolonged hospitalization among seropositive women with acute salpingitis (238). Current recommendations for the treatment of upper genital tract infections are the same as in the general population (220).

Conclusion

We have made great strides in understanding the management of the many gynecologic conditions that affect HIV-positive women with an increased frequency. As the HIV-infected woman’s life expectancy continues to lengthen, we will need new treatments for recurring conditions such as lower genital tract neoplasias. We have much to learn about the interaction between sex steroids, HIV-infection, and the immune system. As our knowledge grows, we will be better equipped to counsel women about contraceptive issues, the menopause and related issues, and pregnancy and infertility.

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