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Care of the Human Immunodeficiency Virus-Infected Menopausal Woman

Helen E. Cejtin, M.D. [Attending Physician, Associate Professor]

John H. Stroger, Jr. Hospital of Cook County

Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine

Abstract

More women than ever before are both Human Immunodeficiency Virus-infected and menopausal, because of increased survival and more frequent diagnosis in older women. Such a woman has the combined burden of her infection, its treatment, comorbid conditions, and aging. Thus she is at risk for a variety of problems such as disorders of bone mineral density and deficiencies in cognitive functioning. In addition to this, she experiences menopause in a unique fashion, with more symptoms and perhaps at an earlier age. The clinician caring for her must take a proactive approach to this multitude of factors that may affect her health and well-being.

Keywords

bone mineral density; cognitive impairment; HIV-infected woman; menopause; vasomotor symptoms

Introduction

Since the widespread use of highly active antiretroviral therapy (HAART), HIV-infection has become a chronic illness. The median survival for a 25 year old diagnosed between 2000 and 2005 is estimated at 39 additional years (1). Thus, there is a steady increase in the number of HIV-infected people who will become 50 years and older, and the Centers for Disease Control (CDC) reports that in the year 2005, 29% of seropositive individuals in the U.S. were in this age group (2). There is an increase in new infections diagnosed in this age group as well, estimated at 19% of all diagnoses in 2005 (2), as opposed to only 10.9% in 2000 (3). This is true for a number of reasons. Since the broader CDC testing recommendations, more older people are being diagnosed (4). Condom use is uncommon in the elderly because of no contraceptive need and a perceived low risk of acquiring infections (5). With the development of medication for erectile dysfunction for men, the elderly are continuing or resuming sexual activity, and a subsequent increase in sexually transmitted infections including HIV has been noted (6). Lastly, changes in the post-menopausal vagina are felt to increase the risk of HIV acquisition during intercourse (7,8). As more women than

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Reprint requests to Helen E. Cejtin, Department of Obstetrics and Gynecology, John H. Stroger Hospital of Cook County 1901 W. Harrison, Chicago, IL 60612 hcejtin@gmail.com Helen E. Cejtin 1935 W. Farwell Chicago, IL 60626 773-761-7763.

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ever will be both menopausal and HIV-positive, it is important to understand this life transition in infected women. They have the additive adverse effects of their infection, its treatment, and their advancing years, increasing the risk of a variety of chronic illnesses. The purpose of this article is to review menopause in the HIV-infected woman; how it presents, its interaction with HIV and comorbid conditions, and the overall management.

Age of Menopause

Menopause has been defined as at least twelve consecutive months of amenorrhea without other obvious causes (9). Most U.S. data about menopause come from studies done on middle class white women, in whom the median age is 50-52 years (10). The Study of Women's Health Across the Nation (SWAN) represented an effort to study menopause in a more diverse group (11). This and other studies demonstrated that women who are African American (12), nulliparous (13), have a lower body mass index (BMI) (13), smoke tobacco (14,15), have more stress (12), less education, and more unemployment (16), experience menopause at an earlier age.

Studies on the effect of HIV on the menstrual cycle are inconclusive (17-21), and use of methadone, illicit substances, and psychotherapeutic medications all cause amenorrhea (22). Of 33 seropositive women aged 20-42, approximately half were anovulatory by luteal progesterone levels, and two were menopausal by follicle stimulating hormone (FSH) >40, indicating a higher prevalence of anovulation but not of early ovarian failure than in the general population (23). Other studies show mixed results regarding the age of menopause in seropositive women and the effect of HIV (24,25). The Women's Interagency HIV Study (WIHS) study of approximately 1400 seropositive and at risk negative women used prolonged amenorrhea, for at least one year, based on semiannual interviews and a serum FSH >25 mIU/ml to define menopause. The median age of menopause was 47 in the entire cohort, and was not associated with serostatus or substance use (26). Among seropositive women with prolonged amenorrhea, 53% had FSH levels less than 25 mIU/ml, implying a cause other than ovarian failure. HIV infection and opiate use were associated with prolonged amenorrhea, but not with menopause, and infected women were three times more likely than controls to have prolonged amenorrhea without ovarian failure (26). In the same cohort, among menstruating women, early follicular phase FSH, estradiol, inhibin B, and Mullerian Inhibiting Factor (MIF) levels were similar in the seropositive and negative women. Thus, HIV infection is not associated with decreased ovarian reserve (27).

HIV seropositive women in this country have many risk factors for early menopause. When compared to women from a similar demographic, however, they do not go through menopause at an earlier age. Although HIV infection per se does not affect ovarian reserve or the age of menopause, it is associated with high rates of prolonged amenorrhea, probably from anovulation secondary to stress, illness, and low BMI. Evaluating menopausal status in such women can be difficult, and a serum FSH level may help clarify the etiology of amenorrhea.

Menopausal Symptoms

There is data to suggest that HIV-positive women have more menopausal symptoms. This can be difficult to ascertain because antiretroviral therapy, comorbidities, and even the infection itself may cause some of the same symptomatology as menopause. HIV-associated dementia can be confused with the memory problems some women experience as they age. AIDS-associated conditions such as tuberculosis or lymphomas can result in night sweats, which may be perceived as hot flashes. Concomitant cocaine use resulting in decreased estrogen levels can result in vaginal dryness (28,29,30), and tobacco use has also been shown to worsen symptoms (31, 32). The sleep disturbances experienced with Efavirenz can

be confused with those seen in perimenopausal women. Data on symptoms in the general population vary greatly, depending on the group studied. Of the plethora of symptoms reported, only vasomotor symptoms and hot flashes are clearly associated with menopausal hormonal changes (32). The variation in symptom prevalence is large across ethnic groups, and older studies of primarily white women report that vasomotor changes affect approximately half (33). Large well-designed studies like the SWAN show that vasomotor instability and vaginal dryness are more prevalent among African Americans, women with increased body mass index (BMI), lower socioeconomic class, and tobacco use (34). We would expect a high degree of symptomatology among seropositive women, who have many of these characteristics. Several studies demonstrate an increase in vasomotor symptoms and vaginal dryness among HIV-infected women present in 64-96% (28,35,36). Increased symptomatology is associated with a positive serostatus as well as with high parity, receiving public aid, depression, increased BMI, experiencing negative life events, and perceiving one's own health as poor (35,36). There is no consistent association between symptoms and disease severity, however (28,35,36, 37).

Symptom reporting may be confounded by incorrect symptom attribution and attitude toward menopause. A study of minority women demonstrated that while most attribute vasomotor symptoms to menopause, less than a third think that it is the cause of their vaginal dryness. Many seropositive women think their symptoms are from their infection or drug use (38). Women who have experienced negative life events have a worse attitude towards menopause, which may make symptoms less tolerable (39,40).

Since the menopausal HIV-seropositive woman is frequently plagued with bothersome symptoms, a discussion of hormone replacement therapy (HRT) is often warranted. One study demonstrated a trend ($p < .06$) toward improved survival among seropositive women who use HRT (41), probably due to confounding factors, with sicker women having more contraindications to hormones. Although HRT probably does not confer a survival benefit to HIV infected women, it should be offered on a short-term basis for relief of significant symptoms (42).

Pharmacokinetic studies demonstrate interactions between hormonal contraception and many antiretroviral medications due to metabolism of both by the CYP3A4 enzyme of the cytochrome p450 system (43), usually resulting in decreased hormone levels. Concomitant use with fosamprenavir, however, yields decreased antiretroviral levels (44). As HRT is similarly metabolized. Similar interactions may occur. Higher doses of HRT may be needed to achieve symptomatic relief. Simultaneous use of fosamprenavir with HRT should be avoided because of the potential for inadequate viral suppression. Because of the increase in cardiovascular disease seen in seropositive patients on antiretrovirals, HRT should be prescribed with caution and should be avoided altogether in women with known ischemic heart disease (45). In our experience, despite an increase in menopausal symptoms in this population, use of HRT is rare, because of pill burden and a fear of drug interactions.

Seropositive women not only have more risk factors for menopausal symptoms, but the infection itself is associated with more symptomatology. It is important to ask specifically about hot flashes and vaginal dryness, as many women will incorrectly attribute these symptoms to their infection or drug use. HRT should be offered for relief of symptoms when not contraindicated. Increased doses may be necessary in women using HAART, and women using Fosamprenavir should avoid HRT.

Sexually Transmitted Infection Screening

In large studies, seropositive women do not have an increased prevalence of sexually transmitted infections (46). When women are co-infected with other sexually transmitted

infections, however, their HIV viral load may increase as well as viral shedding and infectivity (47). Hence, seropositive women should all be screened for treatable sexually transmitted infections including syphilis, gonorrhea, trichomonas, and chlamydia yearly if they are sexually active, and more often with symptoms or high risk behaviors (48).

The seronegative postmenopausal woman with high risk behavior should be counseled about her increased risk of HIV acquisition. Oophorectomized primates receiving vaginal placebo or progesterone acquired Simian Immunodeficiency Virus significantly more frequently than those who received vaginal estrogen, and this is likely secondary to an increased thickness and decreased pH in the epithelium of the estrogen group (49). Serodiscordant couples demonstrate a 4-8 fold increase in HIV acquisition if the woman is postmenopausal (50,51). A recent study of cervical explants from HIV-infected pre- and postmenopausal women demonstrated increased inflammation and HIV-transcription in the postmenopausal women (52). Blood and cervical cells from 24 post- and 21 premenopausal women demonstrated increased expression of CCR5 and other markers of increased susceptibility to HIV in the postmenopausal group (53). This group seems particularly vulnerable to infection and needs to be counseled accordingly.

Cancer screening

Screening guidelines for the general population remain unchanged for seropositive postmenopausal women with the exception of cervical cancer screening (54). The seropositive woman needs yearly cervical cytology for life with the exception of semiannual screening in the year of diagnosis (55). The management of atypical squamous cells of undetermined significance (ASCUS) is also different. Although the use of human papilloma virus testing has been shown to be a cost effective addition in screening seropositive women (56), it is not recommended by the CDC, who states that this population should have colposcopy after a single ASCUS test (55). The benefit of screening immunocompromised women for anal cancer with cytology is unclear (57), but a routine history and physical should involve questions about anal symptoms and a rectal exam.

Bone mineral density disorders

Disorders of bone mineral density are more common in HIV infected women than in their seronegative counterparts. Although the important endpoint is fracture, bone mineral density measurements using dual-energy x-ray absorptiometry (DXA) are the most easily quantified markers that predict fracture risk, and so are the most frequently studied. Studies of infected people of both genders report decreased bone density in 25.7-87.5%, with osteopenia in 22-67.5% and osteoporosis in 1-26.8% (58). A meta-analysis of 20 studies estimates an odds ratio with HIV infection for decreased bone density and osteoporosis of 6.4 and 3.7 respectively (59). The cause is multifactorial, and related to risk factors that are common in this group, the effect of the virus itself, and antiretroviral therapy.

Risks for a decreased bone density include low BMI (60), poor nutrition, inactivity, and use of tobacco (61) and alcohol (62), as well as lesser known risks such as selective serotonin reuptake inhibitor (SSRI) use (63), opiate use (64), coinfection with hepatitis B or C (65), and central obesity (66). Recent data demonstrates a 60-75% prevalence of vitamin D deficiency among HIV-infected individuals, higher in those on Efavirenz (67,68,69). Seropositive women, especially post menopausal, are likely to have many risk factors for low bone density.

Several studies demonstrate that the HIV virus itself affects bone density. Antiretroviral-naïve patients demonstrate decreased density (58), and there is an association between duration of infection and the magnitude of the decrease (70). High viral load (71) and low

CD4+ count (72) are both associated with low bone density. The chronic inflammation associated with HIV infection modulates bone remodeling resulting in osteoclast over osteoblast function (73,74).

The data regarding a role for antiretroviral therapy itself, however, is conflicting (58). A meta-analysis of 10 cross sectional studies demonstrates a reduced density and increase in osteoporosis in antiretroviral-treated subjects compared to controls, with no difference between protease inhibitor (PI)- or non-PI containing regimens (59,75). The most convincing data comes from the Strategies for Management of Anti-Retroviral Therapy (SMART) study. Patients on continuous HIV medication had significantly lower bone density and more fractures than the group getting intermittent therapy (76). There is a loss of density (2-6%), equal to that experienced in the first two years after menopause, when starting antiretrovirals, with subsequent stabilization or improvement (77,78,79). Tenofovir is associated with more initial bone loss than other drugs (80,81), and its action on the proximal renal tubal, causing phosphate wasting, is the probable mechanism (81). All antiretroviral therapy also alter vitamin D metabolism (82).

The data supports an increase in fractures with HIV-infection as well. One study reported a non-significant increase in fractures among infected men (83), while another reported an increase only in men 50 and older (84). Two large studies, however, demonstrate a significant increase in fractures among both infected women and men, although not looking specifically at postmenopausal women (85,69). Few studies of HIV infection and bone density look at women specifically, even fewer at postmenopausal women. One study of postmenopausal minority women demonstrated significantly lower bone mineral density and higher levels of markers of bone turnover among the HIV positive group. HIV infection was an independent predictor of low bone mineral density (86).

Preventive therapy for bone mineral density disorders, as in the general population, includes smoking cessation, adequate nutrition, alcohol reduction to less than 3 drinks daily, weight-bearing exercise, and weight gain if wasting is present. Daily vitamin D (800-1000IU) and calcium (1000-1500mg) supplementation have been associated with an increase in density in the seropositive population (87,61). The bisphosphonates alendronate and zoledronate improve bone density in seropositive individuals without adverse effects (61,68,88). Androgens have been shown to improve density in a small study of HIV infected women (89).

Bone mineral density screening recommendations for HIV-infected women vary. The 2009 European AIDS Clinical Society guidelines (90) recommend a baseline serum 25-hydroxyvitamin D and modified WHO Fracture Risk Assessment Tool (FRAX) using HIV as a secondary risk in women 40 years or older, repeated every 2 years and prior to starting ART (91). The FRAX has never been validated in HIV-infected populations (92). They also recommend a DXA on anyone with a history of a fragility fracture or on steroids for 3 months or longer (90). The Infectious Disease Society of America guidelines recommend a DXA at 50 years only with additional risk factors, repeated every 2-5 years, or at any age with history of a fragility fracture (93). Experts in the field recommend screening any seropositive woman at menopause with a DXA (92).

Seropositive menopausal women have the added effects of their infection, its treatment, and their hypoestrogenic state all making them at very high risk of decreased bone density. They need to rigorously adhere to preventive strategies as well as supplementation and should all be screened at menopause with a DXA scan. Traditional treatment for osteoporosis and osteopenia are effective and safe in this population.

Cognitive Impairment

The spectrum of cognitive impairment seen with HIV infection runs from simple deficits through minor cognitive-motor disorder (MCMD) to full blown HIV-associated dementia (HAD) (94). Some degree of impairment was reported in 68% of older seropositive adults (95), and it impacts everyday functioning and medication adherence (96,97). Age is an important risk factor for dementia, but whether it has a synergistic effect with HIV infection is unclear, and studies have yielded mixed results (98). The impact of HIV on cognition is multifactorial, including an increase in cardiovascular and cerebrovascular disease from both the infection and its treatment, immunologic as well as inflammatory changes, and even testosterone deficiency (98). Similarly, there are risk factors for cognitive impairment that are prevalent in this population (99) such as decreased education (100), psychiatric illness (95), head injury (101), stress (102), chemical dependency, hepatitis C coinfection (103), and advancing age. Lack of antiretroviral therapy use, however, emerges as the most important predictor of cognitive disorders (104,105), and with the introduction of HAART, the incidence of HAD has halved (106,107).

Seropositive women have not been well represented in studies of cognition (108). The Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) demonstrate similar risk of HAD in both genders (109). There is good data to support increased cognitive impairment in infected women compared to seronegative controls (110,105,106), but there is minimal data on cognition in seropositive menopausal women.

In the general population up to 40% of middle-aged women report forgetfulness (111). Although menopause itself does not affect cognition (112,113), vasomotor symptoms and sleep deprivation are associated with memory deficits in seronegative (114) and positive women (115). Hippocampal-dependent memory has been shown to be better in women than men, and to be associated with estrogen levels. Hippocampal blood flow declines with menopause and increases with estrogen therapy (116). HIV infection causes injury to the hippocampus, based on both functional magnetic resonance imaging and autopsy studies (116). Thus one might expect an additive effect of menopause and HIV infection on hippocampal-related cognitive function.

There is a paucity of data on cognition in seropositive menopausal women. Infected women have many comorbid risk factors for cognitive impairment, but HIV infection itself contributes to a range of deficits in both women and men. There is emerging data showing a detrimental effect of the virus on the hippocampus, which may be synergistic with hypoestrogenic effects on hippocampal memory.

Conclusion

As women with HIV infection are living longer and HIV is increasingly being diagnosed in women over 50, the practitioner is likely to see more and more menopausal women with HIV infection. In the pre-HAART era, care of these women involved primarily prophylaxis against opportunistic infections. Because of markedly increased lifespans, their care today involves treating comorbidities associated with the infection and aging as well as heightened prevention and screening strategies.

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