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Gonadal function and reproductive health in women with HIV infection

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Synopsis

Most HIV infections among women occur early in reproductive life, which highlights the importance of understanding the impact of HIV on reproductive functions, and also the potential implications of reproductive function and aging on the course of HIV disease. HIV infection may influence reproductive biology via multiple mechanisms including: potential directs effects on HIV on the hypothalamic-pituitary-gonadal axes, implications of HIV-related immune dysfunction on reproductive biology, effects of antiretroviral treatments on reproductive functions and the impact of treatment related immune reconstitution on reproductive health. Ovarian function is a crucial component of reproductive biology in women, but standard assessment methods are of limited applicability to women with some chronic diseases, such as HIV. New antiretroviral treatments have the potential to increase the ease of conception planning, and to improve fertility. Drug-drug interactions between antiretroviral medications and hormonal contraceptives are potentially significant and merit careful provider attention. While HIV infection is not a major cause of infertility, high level viremia and low CD4 lymphocyte counts are associated with reduced fertility rates. Conception and pregnancy can now be achieved without transmission of HIV to sexual partner or new born, but complications of pregnancy may be more common in HIV infected women than uninfected women.

Keywords

HIV infection; women; sex steroids; reproductive biology

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Introduction

On a global basis, females account for more than 50% of persons living with HIV infection. In 2011 the United States 21% of the estimated 10,257 new HIV diagnoses were made in women, 84% of these were from heterosexual contact[1]. Most HIV infections occur early in women's reproductive life, and thus it is important to consider the impact of HIV on reproductive health and reproductive aging. This chapter will address unique implications of HIV infection on reproductive health throughout a women's lifetime, from the time she enters menarche to menopause with specific impact on the ovulatory cycle, sex steroid hormone production, contraception, fertility, and pregnancy and the implications of gonadal function for the course and outcomes of HIV infection.

Puberty

Information on puberty in HIV-infected girls is based on several U.S. studies that focused on individuals who acquired HIV infection at birth. The most significant differences between HIV infected and uninfected girls occur among individuals who had not received antiretroviral therapy, or what is now considered adequate therapy. In these studies, HIV infection is associated with reduced height attainment, the severity of which was associated with extent of CD4 lymphocyte depletion. [2] No differences in timing of puberty based on HIV status were found in one small U.S. study. [2] The largest analysis of puberty in children with perinatal HIV infection was generated by data combined from large U.S. cohorts, the Adolescent Master Protocol, and the Pediatric AIDS Clinical Trials Group that included findings from 2086 HIV infected children and compared these to 453 HIV exposed but uninfected children[3]. In this larger study, age at puberty (based on Tanner staging) was significantly later in females and males in the HIV infected group (10.5 vs 10 years for females, and 11.5 vs 10.7 years for males, p-values <.0001 for both). Extent of pubertal delay was greatest in children with very high HIV RNA levels and very low CD4+ leukocytes. Antiretroviral treatment was associated with age at puberty that was comparable to uninfected girls.

Any delays in puberty related to HIV infection are likely ameliorated by receipt of effective cART.

Sex steroid levels

Since sex steroids are important immune modulators, the effects of sex steroids on HIV and immune function among HIV infected women are of great interest. Several *in vitro* studies have indicated that estrogen and the estrogen receptor (ER) system can interact with HIV components. For example, Al Harthi and collaborators found that physiological concentrations of 17β-estradiol inhibits HIV replication in peripheral blood mononuclear cells via a mechanism involving β-catenin, TCF-4 and ERα. [4] The Wira group reported that pre-treatment of CD4 lymphocytes and macrophages with 17α-estradiol protected these cells from infection with either CCR-5- or CXCR4-tropic HIV strains via blockage of cell entry; maximal effect occurred at 5×10^{-8}M, a concentration that saturates cellular estrogen receptors. [5] Estradiol treatment after HIV exposure had no effect and ethinyl estradiol did

not demonstrate the same protective action. These findings have potential implications for the selection of steroid components of hormonal contraceptives. However caution must be applied if estrogen, or androgen treatments are to be considered for use in HIV-infected women because HIV itself produces a prothrombotic state, which predisposes HIV patients to thrombotic complications[6].

Multiple studies indicate that sex steroids can interact with HIV components or host responses, but this research is currently of unclear clinical application.

Ovulatory cycle and function

After menarche the ovarian follicle is the major source of sex steroids in nonpregnant, premenopausal women. Steroid synthesis occurs in the single follicle that produces a mature oocyte (the preovulatory and ovulatory follicle) during each ovulatory cycle. Sex steroid production varies by ovulatory cycle phase; a steady state is never achieved. The ovulatory cycle is regulated by neuroendocrine actions that respond to feedback elements produced by the follicle. Sex steroid synthesis is greatly reduced if follicle development and ovulation do not occur. Besides the physiologic anovulatory states prior to menarche and following menopause, anovulation can occur with perturbations of ovarian, hypothalamic or pituitary functions. Chronic illness and disruptions of energy balance can result in anovulation, which is commonly reported in relationship to wasting illnesses, low body fat, receipt of a variety of medications and drugs including cancer chemotherapies[7, 8], immune modulators[9], antiepileptics[10, 11], antipsychotics[10, 12], opioids[13, 14] and others. Several of these factors, such as wasting[15], and use of a variety of medications are common among HIV infected women. Additionally, tobacco use, which is also common among HIV infected women, also can influence levels of neuroendocrine regulators, such as follicle stimulating hormone, FSH[16, 17].

Studies of the effects of HIV infection on ovulation and sex steroid production are challenging to conduct because the measurement of most sex steroids and gonadotropins must be interpreted by ovulatory cycle phase; few studies of the effects of HIV infection on ovulatory functions have utilized methods that enable cycle phase interpretation of steroid and gonadotropin levels. Data from women with irregular menstrual cycles may be particularly difficult to interpret. Furthermore, effects of HIV must be differentiated from that of conditions and treatments that are common among HIV-infected women, such as use of opioids and loss of fat mass.

HIV infected women are at increased risk for secondary amenorrhea due to:

- Loss of body fat
- Use of drugs associated with amenorrhea, such as psychiatric and seizure medications, cancer chemotherapies, immune modulators, and long term opioids.

The Women's Interagency HIV Study (WIHS), a large observational cohort study of U.S. women with, or at high risk for, HIV infection, conducted evaluations of sex steroid levels among women with regular menstrual cycles, who did not receive exogenous sex steroids, and who underwent sample collection during the early follicular ovulatory phase [18]. The

HIV infected women varied widely in their CD4 lymphocyte counts and plasma HIV RNA levels. Estradiol levels were 37.0 pg/mL (95% CI 27.0, 51.0) in the HIV infected women versus 43.5 pg/mL (31.0, 58.0) in the uninfected women, a difference that was statistically significant at the p=.001 level. There was no statistically significant difference in inhibin-b and follicle stimulating hormone (FSH) levels between the two groups. The study measured dehydroepiandrosterone sulfate (DHEAS), testosterone and sex hormone binding globulin (SHBG) levels at times not determined by ovulatory phase and found that HIV infection was associated with statistically significant differences in all three measures (mean DHEAS in HIV infected women was 73.3 μg/dL (34.0, 123) versus in uninfected women 106.0 μg/dL (65.0, 165), p<.0001), mean testosterone in HIV infected women was 22.7 ng/dL (10.0, 36.9) versus in uninfected women 37.3 ng/dL (22.7, 53.1), p<.0001) and mean SHBG in HIV infected women was significantly higher 58.5 nmol/L (41.0, 88.0) versus in uninfected women 47.0 nmol/L (32.0, 70.0), p<.0001. Use or nonuse of combination antiretroviral regimens and controlling for age, smoking, body mass, and drug use did not influence the hormonal measures in this study, indicating that HIV infection may be associated with reduced sex steroid levels. By contrast, Weinberg and colleagues studied sex steroid levels in 20 HIV infected and 20 HIV uninfected nonpregnant, not receiving exogenous sex steroids and women with regular menstrual cycles at three timepoints after menses.[19] The HIV infected group had CD4 lymphocyte counts ≥300cells/μL and plasma HIV RNA levels <10,000 copies/mL. No significance differences in estradiol and progesterone levels were found between the HIV infected and uninfected groups. The discordant results may be due to differences in sample size, but more likely to the higher CD4 cell counts and lower HIV RNA levels in the Weinberg versus the WIHS studies, indicating that HIV disease status may influence sex steroid levels.

Clark and colleagues examined FSH and self-reported menstrual pattern among 24 HIV infected women aged 20–42 years who had participated in AIDS Clinical Trials Group studies prior to 2000 and who had advanced HIV disease. They found that most women had normal FSH levels, but that 48% of the group had not experienced menses in 90 days, which indicated a very high occurrence of anovulation. Another study examined 14 HIV infected WIHS participants, aged 19–44 years, who reported regular menstrual cycles and who provided weekly blood samples, 28% of women experienced anovulation as determined by endocrine criteria including early follicular phase estradiol and FSH, periovulatory luteinizing hormone, and midluteal progesterone levels[20]. These studies may indicate that anovulation is associated with extent of HIV morbidity, but the small sample size is a significant limitation.

Menopause

Menopause is defined by the final menstrual period experienced by a woman, and is preceded by variability in cycle length and eventually periods of amenorrhea lasting ≥60 days. [21] The World Health Organization defines menopause as 12 consecutive months without menstruation, with the date of menopause occurring at the end of the year of amenorrhea. [22] Interpretation of published findings on the impact of HIV infection on the age of menopause depends on the how menopause is defined, and whether one considers self-reported amenorrhea to be a reliable indicator of menopause in a chronically ill

population. Studies that utilize self-reported amenorrhea of 12 months duration as criteria for menopause tend to find that HIV infection is associated with menopause at an earlier age than occurs among uninfected women. [23, 24] Earlier age at menopause is associated with low[25] or higher[26] CD4 lymphocyte counts and recreational drug use.[25–27]

In middle age, women who experience prolonged amenorrhea may report menopause regardless of whether physiologic tests of ovarian reserve (primary and secondary follicles that are capable of forming an ovulatory follicle) have been done to confirm menopause. Cejtin published from the WIHS that more than 50% of HIV infected women who reported ≥12 months of amenorrhea did not have FSH levels of more than 25mIU/mL, indicating that protracted amenorrhea was common in the absence of menopause in this large study. [28] Thus, given the frequency of amenorrhea in association with HIV infection, determination of the relationship between HIV infection and age at menopause supports the use of biologic measures of menopause. Seifer and colleagues completed two analyses of HIV-infected and uninfected WIHS participants who had regular menstrual cycles and who were sampled during the early follicular phase and found no statistically significant difference by HIV status in age at which biological measures indicated diminished ovarian reserve, which is an essential feature of menopause. [29,30] Overall there is little indication that HIV infection itself is associated with an earlier age at menopause, but rather, it appears that HIV, and HIV morbidity, is associated with amenorrhea. It should be noted that prolonged anovulation and amenorrhea both share some medical outcomes with menopause, for example, risk of bone demineralization, so that that ovulatory dysfunction in HIV infection may have significant health implications.

Fertility

Some studies indicate that HIV-infected women who are not receiving antiretroviral treatment may have decreased fertility compared with their uninfected counterparts[31, 32]. As a sexually transmitted infection, HIV is also epidemiologically associated with the occurrence of other STIs, some of which cause pelvic inflammatory disease, which in turn may cause tubal factor infertility. Additionally some AIDS defining conditions, such as tuberculosis or lymphoma, or their treatment, may adversely impact fertility. [33] The odds of pregnancy are greatest in women with less severe HIV morbidity as indicated by disease stage[34], higher CD4 cell count[35] and lower number of copies of HIV RNA in plasma (viral load) [36, 37]. Receipt of potent antiretroviral therapy regimens is associated with increased fertility, an effect that is likely related to the woman's choice in view of a good prognosis[38], and the increased CD4 cell counts and decreased viral load that results from therapy.[35]

Conception

Significant concerns are often expressed regarding the risk of HIV transmission in couples with one HIV infected partner. Greater HIV disease infirmity, lower CD4 lymphocyte counts, and increased HIV RNA in plasma or genital fluids are associated with increased likelihood of HIV transmission. The efficacy of potent antiretroviral regimens in suppressing HIV replication and resultant viremia and shedding of virus in genital secretions has changed the approach to prevention of transmission of HIV in couples who are

discordant for infection. A large number of studies has demonstrated that treatment of the HIV infected partner with potent antiretroviral regimens (combined antiretroviral therapies, or cART) and suppression of detectable viremia results in a high degree of protection from sexual HIV transmission. [39, 40] Computational models indicate that reduction in plasma HIV RNA levels to less than 100 copies decreases heterosexual transmission by 91% (79–96%).[41] The risk of transmission approaches zero when analysis is limited to cART recipients who succeed in dropping HIV RNA below level of assay detection (less than 50 copies per ml of plasma).[42] Additional protection can be provided by pre-exposure treatment of the uninfected partner (so-called PREP) in which an uninfected individual who is at risk for the sexual acquisition of HIV, consistently takes a regimen of two antiretroviral nucleosides to prevent transmission[43–45]. Other options for reduction of transmission risk include the use of insemination with processing of semen to wash sperm and eliminate leukocytes[46–48], and general care for reproductive health issues, such as any sexual transmitted infections. [43, 49]

Pregnancy

Prior to the introduction of effective antiretroviral therapy, approximately one quarter of pregnancies among HIV infected women resulted in transmission to their newborns[50]. The first great success in the prevention of HIV transmission was reported in 1994, with demonstration that azidothymidine, a single nucleoside, was effective in reducing transmission to 8.3% of births. Since that time use of cART has shown to be virtually 100% effective in prevention of transmission from mother to infant, when maternal treatment is initiated during pregnancy and plasma HIV RNA is below assay detection. [51] It is now common for HIV infected women to contemplate pregnancy with the expectation of a healthy infant, and the outcomes of pregnancy among HIV infected women are generally quite good. Elective cesarean section is recommended for women with HIV RNA levels greater than 50 copies /mL prior to onset of labor. [51] Several concerns regarding pregnancy complications in HIV infected women have arisen, including some evidence of increase occurrence of pre-eclampsia, gestational diabetes and low infant birth weight. While initial concerns were focused on the possible role of antiretroviral drugs in pre-eclampsia, more recent data from Botswana indicate that pre-eclampsia in HIV infected women is independently associated with high pretreatment plasma HIV RNA levels and low levels of placental growth factor. [52] The Frankfort HIV Cohort group reported that in the cART era, pre-term birth among HIV infected women declined compared with earlier times, but pre-eclampsia, gestational diabetes did not change with the advent of cART, and remained more common than that reported for the general population. [53] These findings are not definitive, but support the current recommendations that HIV infected pregnant women receive careful prenatal care including provision of cART.

Contraception

Research on contraception and HIV infection has largely focused on two topics: the potential effects of hormonal contraceptives on susceptibility to HIV infection, and the impact of antiretroviral drugs on hormonal contraceptive effectiveness.

HIV susceptibility

Because hormonal contraceptives are among the most commonly used medications globally, and users tend to be young, sexually active women, the impact of hormonal contraceptive exposure on risk of HIV infection has been the focus of multiple research studies. Overall the research findings are not conclusive and even in studies that indicate exposure to contraceptive steroids may confer risk, the effect size is modest. The greatest concern regards depot injectable medroxyprogesterone acetate, DMPA or "DepoProvera", which is a widely used, inexpensive and effective contraceptive. The consensus is that combination oral contraceptives likely have no effect on HIV susceptibility. With regards to DMPA, no consensus has been reached, and study findings are mixed[54]. DMPA has significant glucocorticoid mimetic effects and which could influence HIV susceptibility[55]. Several alternative contraceptive progestins, do not influence HIV viral effects that are mediated via the glucocorticoid receptor; DMPA does[56]. However studies of human vaginal histology do not indicate that DMPA produces epithelial thinning[57], which was postulated as a basis for increased risk with this contraceptive. Overall, careful review of current research provides no clear answer[58], and a switch from DMPA to oral contraceptives has significant monetary and social disadvantages[59].

The contradictory evidence related to hormonal contraceptives and increased susceptibility to HIV infection most often implicates DMPA, but the effect size is quite small. The high efficacy and low cost of this contraceptive must be taken into consideration as well.

Contraceptive effectiveness

Because many antiretroviral drugs, particularly protease inhibitors and non-nucleoside reverse transcriptase inhibitors, can influence the activity of key drug metabolism pathways, drug-drug interactions between hormonal contraceptives and antiretroviral treatments (ART) are possible. Of greatest concern is the potential for ART to decrease levels of contraceptive estrogens and progestins resulting in contraceptive failure, though most studies focus on pharmacological endpoints, and not contraceptive efficacy[60]. El-Ibiary and Cocohoba reviewed studies dated to 2006[61] and identified many potential interactions, which are specific to both the antiretroviral drug and to the steroid component of the contraceptive. In general, the greatest concern occurred in the setting of regimens that contain ritonavir, a protease inhibitor that is a potent inducer and inhibitor of several metabolic enzymes, but the authors noted that more research is greatly needed. Robinson and colleagues did a similar analysis to 2012 but did not focus on the effects of concurrent ritonavir. The noted that DMPA and the levonorgestrel intrauterine system both were relatively free of interactions with ART[62] Nanda et all studied 402 premenopausal South African women and found no significant effect if nevirapine on the efficacy of low dose combination oral contraceptives[63]. Landolt and colleagues similarly found that nevirapine did not adversely influence levels of contraceptive progestins, but efavirenz did in a relatively small study of Thai women[64] but DMPA levels and break-through ovulation were not influenced by efavirenz in another study[65]. Limited data indicate that hormonal contraceptives do not adversely influence ARV levels, though the range of such studies is quite limited[60].

Conclusion

The availability of potent combination antiretroviral therapies has greatly improved the overall health and survival of HIV infected women. Access to and use of cART is the major predictor of outcome of HIV infection among women. Many questions remain to be answered related to the impact of menopause on the course of HIV infection, whether contraceptive steroids influence risk of HIV transmission, or alter concentrations of antiretroviral drugs. Additionally, while conception can be achieved without transmission of HIV to an uninfected partner and to the newborn, further research is needed to determine whether complications of pregnancy such as pre-eclampsia and gestational diabetes are more common among HIV infected women, and if so, how HIV infection, or its treatment contributes to these pathogenic conditions.

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Key Points

- Reproductive health in HIV infection is associated with extent of HIV morbidity; women who receive antiretroviral treatment, suppress viremia and have normal CD4 lymphocyte counts, generally have normal reproductive function;
- Hormonal contraceptives are generally safe, but some debate persists regarding the effects of certain progestins in increasing susceptibility to HIV infection, though the effect size, if this interaction exists, is small;
- There is little evidence that HIV infection causes early menopause, but protracted amenorrhea can be common, particularly among women with advanced HIV disease;
- Complications of pregnancy, such as pre-eclampsia and gestational diabetes may be more common among HIV infected women, though much more research is needed to evaluate this.
- Puberty occurs normally in HIV infected girls, though height attainment may be lessened, later puberty can occur in girls with HIV viremia and CD4 lymphocyte depletion.