Gonadal Function and Reproductive Health in Women with Human Immunodeficiency Virus Infection

Swaytha Yalamanchi, MD[a], Adrian Dobs, MD[a],
Ruth M. Greenblatt, MD[b,c,d,*]

KEYWORDS

• HIV infection • Women • Sex steroids • Reproductive biology

KEY POINTS

- Reproductive health in human immunodeficiency virus (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, although 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 preeclampsia and gestational diabetes may be more common among women infected with HIV, although more research is needed to evaluate this.
- Puberty occurs normally in girls infected with HIV, and although height attainment may be lessened, later puberty can occur in girls with HIV viremia and CD4 lymphocyte depletion.

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[a] Department of Endocrinology, Diabetes and Metabolism, Johns Hopkins University School of Medicine, 1830 Monument Street, Baltimore, MD 21287, USA; [b] Department of Clinical Pharmacy, University of California, San Francisco Schools of Pharmacy and Medicine, 405 Irving Street, Second Floor, San Francisco, CA 94122, USA; [c] Department of Medicine, University of California, San Francisco Schools of Pharmacy and Medicine, 405 Irving Street, Second Floor, San Francisco, CA 94122, USA; [d] Department of Epidemiology and Biostatistics, University of California, San Francisco Schools of Pharmacy and Medicine, 405 Irving Street, Second Floor, San Francisco, CA 94122, USA
* Corresponding author. 405 Irving Street, Second Floor, San Francisco, CA 94122.
E-mail address: ruth.greenblatt@ucsf.edu

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INTRODUCTION

On a global basis, women account for more than 50% of persons living with human immunodeficiency virus (HIV) infection. In 2011 in the United States, 21% of the estimated 10,257 new HIV diagnoses were made in women, and 84% of these were from heterosexual contact.[1] Most HIV infections occur early in women's reproductive lives, and thus it is important to consider the impact of HIV on reproductive health and reproductive aging. This article addresses the unique implications of HIV infection on reproductive health throughout women's lifetimes, from the time they enter 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 girls infected with HIV is based on several US studies that focused on individuals who acquired HIV infection at birth. The most significant differences between girls who are and are not infected with HIV occur among individuals who had not received antiretroviral therapy, or what is now considered adequate therapy. In these studies, HIV infection was 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 1 small US study.[2] The largest analysis of puberty in children with perinatal HIV infection was generated by data combined from large US cohorts, the Adolescent Master Protocol, and the Pediatric AIDS (acquired immunodeficiency syndrome) Clinical Trials Group, which included findings from 2086 children who were infected with HIV and compared these with 453 children who were exposed to HIV but not infected.[3] In this larger study, age at puberty (based on Tanner staging) was significantly later in girls and boys in the group infected with HIV (10.5 vs 10 years for girls, and 11.5 vs 10.7 years for boys, *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 with uninfected girls.

> Any delays in puberty related to HIV infection are likely ameliorated by receipt of effective combined antiretroviral therapies (cART).

SEX STEROID LEVELS

Because sex steroids are important immune modulators, the effects of sex steroids on HIV and immune function among women infected with HIV 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, Szotek and colleagues[4] found that physiologic concentrations of 17beta-estradiol inhibit HIV replication in peripheral blood mononuclear cells via a mechanism involving beta-catenin, transcription factor 4 (TCF-4), and ERα. The Wira group reported that pretreatment of CD4 lymphocytes and macrophages with 17ss-estradiol protected these cells from infection with either C-C chemokine receptor type 5 (CCR-5) –tropic or C-X-C chemokine receptor type 4 (CXCR4)–tropic HIV strains via blockage of cell entry; maximal effect occurred at 5×10^{-8}M, a concentration that saturates cellular ERs.[5] Estradiol treatment after HIV exposure had no effect and ethinyl estradiol did not show the same protective action. These findings have potential implications for the selection of steroid