Good News for Women Living with HIV

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(See the article by Tai et al., on pages 1044–52.)

Early in the epidemic of AIDS, when we were just recognizing its existence and transmission patterns—as well as not so early, during the long years before truly effective therapy was developed—many women with HIV infection or AIDS were told by their physicians that it would be immoral for them to become pregnant, because there was an ~25% risk of transmitting their illness to their infants. The official recommendation was that women "delay" childbearing [1]. At the time, we did not know whether a woman's own HIV disease would progress more rapidly because of pregnancy, but we—and she—could be nearly certain that, if she were symptomatic because of HIV infection, she herself would not live past the child's early years. We have traveled a long road since then. Our understanding of HIV pathophysiology, our ability to identify the predictors of mother-to-child transmission (MTCT), and, most importantly, our ability to prevent or reverse HIV-induced immunodeficiency in those infected and to prevent MTCT have favorably have altered many aspects of HIV infection, including its impact on women's and couples' decision making regarding childbearing.

Motherhood is of great importance to many, and perhaps most, women. For many HIV-infected women before the advent of highly active antiretroviral therapy (HAART), there was great pain in deciding whether to have or not have a child, in caring for a child through an HIV-caused illness that usually culminated in death, and in knowing that she would likely not live to protect her HIV-uninfected children and guide them to adulthood. This emotional landscape changed dramatically during the early 1990s, when administration of zidovudine during pregnancy, labor, and delivery and for 6 weeks postnatally to the infant reduced MTCT of HIV by 70% [2]. Currently, nearly all MTCT can be prevented by the administration of appropriate HAART regimens during pregnancy and delivery, with postnatal treatment for the infant [3, 4]. Many women who had delayed childbearing subsequently considered having children, because the risk of transmitting HIV could be minimized.

However, we do not know the effect of pregnancy on the progression of HIV disease, especially in women who receive HAART either to treat their own disease or solely to prevent MTCT. The concern has mostly been that pregnancy may cause more rapid disease progression. Reports before the availability of HAART were inconclusive: although early studies in higher-resource countries found a slightly increased risk of faster progression [5], later studies (still in the pre-HAART era) demonstrated no effect [6, 7]. In lower-resource settings, pregnancy was associated with faster progression in some studies [8, 9], but it may have represented non-HIV pregnancy-related morbidity and mortality. In this issue of the *Journal,* Tai et al. [10] from Vanderbilt University provide information of great importance to HIV-infected women. Not only was pregnancy *not* found to be associated with more rapid progression of HIV disease, it in fact had a marked protective effect. Among 759 women entering care for HIV infection from 1 January 1997 through 31 December 2004, the 139 women who had 1 or more pregnancies (there were 174 total pregnancies, nearly all of which culminated in live birth) experienced an AIDS-defining illness or died 10%–40% as often as the women who did not become pregnant. The pregnant women differed from the nonpregnant women in predictable parameters, many of which would bias the results toward improved disease-free survival: the pregnant women were younger, had higher $CD4^+$ lymphocyte counts, received more intensive health care, and were more likely to receive HAART and to be adherent to therapy while pregnant. In addition to standard multivariate analyses, the authors performed multiple subanalyses in an effort to tease out the effects of these potential confounders: not only did these not obviate the protective

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effect of pregnancy, they demonstrated at least as large an association. Because these findings will provoke skepticism in many and incredulity in some, it is worth reviewing these analyses in detail.

The authors performed a subanalysis in which pregnant and nonpregnant women were matched by age, date, and $CD4^+$ lymphocyte count at entry into care and subsequent receipt of HAART. The inclusion of HAART in this analysis is important. Other than HAART, the factors distinguishing the 2 groups rarely confer a protective effect similar in magnitude to the hazard ratio (HR) of 0.40 demonstrated by Tai et al. for pregnancy (the difference between the groups in median $CD4^+$ lymphocyte count was <100 cells/μL). In this age-matched analysis, the HR for disease progression in pregnant compared with nonpregnant women was 0.10, with a 95% confidence interval that overlapped that of the primary analysis—which does not necessarily indicate a greater protective effect of pregnancy than in the primary analysis, but it certainly does not indicate an attenuated effect. In addition, by developing a pregnancy propensity score for the factors most associated with pregnancy in their own data, the authors performed analyses that adjusted for those factors associated with the likelihood of becoming pregnant. Adding the propensity score to the multivariate analyses barely altered the magnitude (HR) or the strength (*P* value) of the association.

In the past, normal pregnancy has been described as an immune-suppressed state that is induced so that the fetus would not be rejected by the mother's immune system. However, more recent evidence indicates that the immunology of both pregnancy and the sex steroid hormones is exceedingly complex and not yet well understood. The fetus is likely protected not by immune suppression in the mother but by changes in HLA expression in the trophoblast [11]. The maternal response is controlled immune activation, both at the placenta-trophoblast interface and systemically. As Tai et al. note, there is a shift from a predominately Th1 to a Th2 response [11–13]. Some believe that this shift in the adaptive immune system is necessary to maintain a normal pregnancy [12], whereas others suggest that NK cells (the innate immune system) are the critical factor [13]. These responses may provide a survival advantage, albeit short-lived, through immune activation. This speculative interpretation would also explain the trend toward the increased protection conferred by multiple pregnancies found by Tai et al.

Normal pregnancy is a state of extraordinary hormonal change, with no parallel in normal human physiology. Levels of estradiol, estriol, estrone, and progesterone increase 100- to 1000-fold [14]. Serum concentrations of human chorionic gonadotropin, barely detectable in nonpregnant woman, increase to >100,000 mIU/mL [14]. It has only recently become apparent how extensive the effects of the sex steroid hormones (estrogens, progestins, and androgens) on multiple physiologic processes are. For example, in an in vitro model using the murine lacrimal gland, progesterone induces the expression of nearly 500 genes, including many that are involved in the immune system [15]. Estrogens have been found to influence tumor necrosis factor–α and interleukin-10 production and to induce apoptosis [16]. During the last decade, there has been an explosion of research on the maternal immune response during pregnancy. To date, however, there is an incomplete understanding of the complexity of the immune response and the effects of the profound hormonal changes that occur during pregnancy. The findings of Tai et al. suggest that fruitful communication can occur between those investigating the immune response during pregnancy and those assessing the influence of pregnancy on HIV disease progression, given that each may inform the work of the other.

Worldwide, the greatest burden of HIV infection is carried by poor women in lower-resource communities [17], who generally bear more children than most women in the United States. They may thus experience a stronger protective effect of pregnancy. However, maternal morbidity and mortality are markedly higher than those in higher-resource settings [18], and any protective effect of pregnancy may be lost in the larger burden of non-HIV disease. As programs are developed to provide HAART both for prevention of MTCT and for treatment of HIV-induced immune suppression, it will be important to determine the impact of pregnancy in these settings. The potential interaction between HAART and pregnancy is one more reason to strive to ensure that prevention of MTCT means providing HAART, not a therapy of lesser efficacy, and to support international programs whose goal is to reduce maternal mortality.

In summary, for women in higher-resource settings and perhaps for women in lower-resource settings, the findings reported by Tai et al. in this issue of the *Journal* are extremely important. Such women can now have greater confidence that, in addition to protecting their children from MTCT with HAART, their own health will not be compromised by pregnancy, which would place their children at long-term risk. For all women, pregnancy is something of a gamble: there is no guarantee of a normal pregnancy or a healthy baby. For HIV-infected women becoming pregnant, the findings of Tai et al. suggest that, at least for HIV disease progression, the odds may be in their favor.

References

1. Centers for Disease Control. Recommendations for assisting in the prevention of the perinatal transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus and acquired immunodeficiency syndrome. MMWR Morb Mortal Wkly Rep **1985**; 34:721–6, 731–2.
2. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with

zidovudine treatment. N Engl J Med **1994**; 331:1173–80.
3. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. JAMA **2000**; 284:190–7.
4. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clin Infect Dis **2005**; 40:458–65.
5. Biggar RJ, Pahwa S, Minkoff H, et al. Immunosuppression in pregnant women infected with human immunodeficiency virus. Am J Obstet Gynecol **1989**; 161:1239–44.
6. Alliegro MB, Dorrucci M, Phillips AN, et al. Incidence and consequences of pregnancy in women with known duration of HIV infection. Italian Seroconversion Study Group. Arch Intern Med **1997**; 157:2585–90.
7. Bessinger R, Clark R, Kissinger P, Rice J, Coughlin S. Pregnancy is not associated with the progression of HIV disease in women attending an HIV outpatient program. Am J Epidemiol **1998**; 147:434–40.
8. Deschamps MM, Pape JW, Desvarieux M, et al. A prospective study of HIV-seropositive asymptomatic women of childbearing age in a developing country. J Acquir Immune Defic Syndr **1993**; 6:446–51.
9. Kumar RM, Uduman SA, Khurrana AK. Impact of pregnancy on maternal AIDS. J Reprod Med **1997**; 42:429–34.
10. Tai JH, Udoji MA, Barkanic G, et al. Pregnancy and HIV disease progression during the era of highly active antiretroviral therapy. J Infect Dis **2007**; 196:1044–52 (in this issue).
11. Szekeres-Bartho J. Immunological relationship between the mother and the fetus. Int Rev Immunol **2002**; 21:471–95.
12. Hunt JS. Stranger in a strange land. Immunol Rev **2006**; 213:36–47.
13. Sargent IL, Borzychowski AM, Redman CW. NK cells and human pregnancy—an inflammatory view. Trends Immunol **2006**; 27: 399–404.
14. Williams Obstetrics online. Available at: http://www.accessmedicine.com/. Accessed 13 April 2007.
15. Suzuki T, Schirra F, Richards SM, et al. Estrogen's and progesterone's impact on gene expression in the mouse lacrimal gland. Invest Ophthalmol Vis Sci **2006**; 47:158–68.
16. Carruba G, D'Agostino P, Miele M, et al. Estrogen regulates cytokine production and apoptosis in PMA-differentiated, macrophage-like U937 cells. J Cell Biochem **2003**; 90: 187–96.
17. United Nations Joint Programme on HIV/AIDS. Report on the global AIDS epidemic 2006. Available at: http://www.unaids.org/en/HIV_data/epi2006/default.asp. Accessed 15 April 2007.
18. United Nations Development Program. Human development report 2006. Available at: http://hdr.undp.org/hdr2006/statistics/indicators/98.html. Accessed 15 April 2007.