Human immunodeficiency virus and infertility treatment

The Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Human immunodeficiency virus is a serious but manageable chronic disease that affects persons of reproductive age, many of whom express a desire for biologic parenthood. This document is a revision of the original document of the same name, published in 2002 and reviewed in 2006. (Fertil Steril® 2010;94:11–5. ©2010 by American Society for Reproductive Medicine.)

SUMMARY

1. Human immunodeficiency virus (HIV) is a serious but manageable chronic disease that affects persons of reproductive age, many of whom express a desire for biologic parenthood.
2. Current treatments for HIV can limit the risk of viral transmission to partner and offspring. Recent studies show that in HIV-infected women, the use of antiretroviral therapy, delivery by cesarean section, and avoidance of breast-feeding reduce the chance of newborn infection to ~2%.
3. In couples in which the man is HIV infected, the use of sperm preparation techniques coupled with either inseminations or IVF with ICSI has proven to be highly effective in avoiding seroconversion of uninfected women and offspring.
4. Fertility clinics, to the extent it is economically and technically feasible, should offer services to HIV-infected individuals and couples who are willing to use risk-reducing therapies.

INTRODUCTION

Human immunodeficiency virus (HIV) has infected people of all ages. The largest group affected (86%) are persons of active reproductive age (15–44 years old), about one-third of whom report the desire to have children. This fact underscores the concern of viral transmission to sexual partners and offspring. Because women make up ~20% of cases, and because HIV has become more prevalent among heterosexual couples than in the past, some infected persons will probably ask their health care providers for advice about and assistance with having children who are free of the virus.

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No reprints will be available.

In 1994, the Ethics Committee of the American Society for Reproductive Medicine (ASRM) set forth guidelines concerning patients with HIV who may request or need reproductive assistance (1). The Committee expressed concern about potential transmission of the virus to an uninfected partner or to the couple's offspring. It also addressed potential problems for the child related to the shortened life span of one or both infected parents. On the basis of these concerns, the Committee recommended that testing for the presence of the virus be offered to all couples requesting reproductive assistance. The Committee also recommended that institutions establish their own written policies on infertility treatment for people infected with HIV. It suggested that physicians counsel couples about the consequences of using potentially infected sperm and discuss the options of donor sperm, adoption, or not having children.

When these guidelines were published in 1994, HIV infection was considered to be a serious contraindication to establishment of a healthy pregnancy. Since then, understanding and treatment of HIV-infected persons and laboratory techniques for the preparation of virus-free sperm for reproductive assistance have improved substantially (2–5). With more effective treatment regimens, the death rate has decreased dramatically among persons who become infected, converting HIV from a deadly disease to a manageable chronic illness that much less commonly results in death.

Several methods of limiting the risk for HIV transmission to partner and offspring have also been developed. For example, zidovudine has reduced the vertical transmission of infection from 16%–24% to 5%–8% when given to HIV-infected pregnant women during the second and third trimesters and to their newborns for 6 weeks (4, 6–8). More recent clinical trials demonstrate that combination antiretroviral treatment given to HIV-infected women antenatally further reduces transmission to offspring to <2% (9).

A meta-analysis of studies conducted in North America and Europe concluded that elective (planned) cesarean section added to antiviral treatment would decrease the vertical transmission rate to 2% compared with 7.6% in children of treated women who deliver vaginally. Subsequent studies have found that cesarean section is not needed to lower the risk of transmission if viral levels in the pregnant woman are undetectable (10–12).

Lack of apparent transmission of HIV to partner or child with intrauterine insemination (IUI), or with IVF with intracytoplasmic sperm injection (ICSI) has been reported for discordant (male-positive) couples. Highly active antiretroviral therapy can reduce the

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viral burden in a person's serum and semen. Testing of sperm by using a polymerase chain reaction assay has improved the ability to determine whether the virus is present in the washed sperm preparation (4, 5, 13–15).

In light of these changes in the treatment and reproductive consequences for men and women who are HIV infected, the Ethics Committee reexamined its earlier guidelines. This paper addresses ethical issues concerning: 1) infertility treatment when one partner is HIV infected; 2) infertility treatment when both partners are infected; 3) knowingly conceiving a child who may be born with HIV; 4) HIV testing for couples seeking fertility assistance; and 5) potential risks to the caregivers of patients who are HIV infected.

INFERTILITY TREATMENT WHEN ONE PARTNER IS HIV POSITIVE

The presence of HIV may not affect the reproductive potential of a seropositive person unless he or she is ill due to an opportunistic infection. The HIV transmission rate to an uninfected partner is estimated to be ~1 in 500–1,000 episodes of unprotected intercourse (16). The risk of viral transmission increases dramatically if the HIV-infected partner's viral load is high or if the HIV-uninfected partner has a concomitant genital infection, inflammation, or abrasions.

If a woman is HIV infected and her male partner is HIV uninfected, transmission of infection to the male partner can be avoided by using homologous insemination with the partner's sperm. The resulting pregnancy may still pose some risk to the HIV-infected woman and her child, because opportunistic infections occurring during pregnancy can be devastating to the woman and fetus. An HIV-infected woman may require certain medications in the early stages of pregnancy that could have adverse effects on a developing fetus. Amniocentesis, a procedure commonly recommended to women older than 35 years of age, carries the risk of viral transmission to the fetus as the needle is passed through the HIV-infected woman's abdominal cavity into the amniotic sac.

If an HIV-infected pregnant woman is not actively treated with antiviral drugs, the risk of HIV transmission to the infant is >20% regardless of the viral load. As noted, administration of zidovudine to pregnant women and to newborns during the first 6 weeks of life can substantially reduce the risk of HIV transmission to 5%–8%. Administration of combination antiretroviral therapy, delivery by cesarean section and avoidance of breast-feeding may further reduce the chance of infection to ~2% (4, 6–9).

Attempts at conception between HIV-infected men and their HIV-uninfected female partners that rely on using condoms except at the time of ovulation appear to reduce, but not eliminate the risk of seroconversion compared with complete avoidance of condom use. The seroconversion rate was 4.3% in one study of 92 HIV-uninfected women with HIV-infected partners trying to establish pregnancies through timed intercourse. Two of the women in that study seroconverted during pregnancy, and another two converted in the postpartum period. Those four women reported inconsistent condom use by their partners (14). Even though some HIV-discordant couples have established pregnancies through timed unprotected intercourse without infecting the uninfected partner or child, this practice is unsafe and is not recommended.

Several reports have described specific methods for sperm preparation and testing that can substantially reduce the chance of HIV transmission to the female partner and child. In 1998, Semprini et al. (4) reported using a density gradient and swim-up technique to obtain sperm, which were then tested by polymerase chain reaction assays for the presence of HIV. If the final sperm sample tested negative on these assays, it was used for insemination. With this technique, <1% of the samples (6 out of 623) tested positive for the virus and were not used.

Semprini et al. reported almost 1,600 inseminations of 513 HIV-uninfected women, from which 228 pregnancies resulted. A follow-up of 97.5% of the women at 3 months and 92% at 1 year revealed that all children older than 3 months of age and all mothers tested were HIV uninfected (4). Current world data on the use of IUI for HIV-serodiscordant couples shows that of 1,097 patients in which 2,988 cycles were performed, there were no infections in either the HIV-uninfected female or any of the offspring (13). Even with these data showing no seroconversions using IUI and sperm preparation, more sensitive methods to isolate noninfected sperm are currently being tested for clinical use (3).

Recent data on the use of IVF with ICSI are promising in terms of avoiding transmission to uninfected women. In a 10-year retrospective review of a program offering assisted reproductive technologies (ART) to HIV-discordant couples, 181 couples underwent treatment with IVF with ICSI in which sperm was prepared using a modified density gradient centrifugation and swim-up method. As a result, there were 116 deliveries of 170 neonates (due to a multiple birth rate of 41%). There were no female seroconversions and no infections noted in any of the offspring (14).

These statistics are reassuring, particularly because the seroconversion rate with unprotected intercourse is low but extant. More data are needed to demonstrate the complete efficacy of these techniques. Until then, couples must still be cautioned about the potential risk of HIV transmission to the uninfected partner and to their offspring. Couples seeking the safest methods to prevent transmission of the virus when the male partner is HIV infected should be counseled about using donor sperm, considering adoption, or not having children.

When male-positive discordant couples want to have their own genetically related children, they should be informed of available risk-reduction techniques and encouraged to seek assistance at institutions that can provide the most effective methods of sperm preparation, as well as appropriate testing and treatment necessary to minimize the chance of HIV transmission to partner and offspring. To determine the true efficacy of the chosen method of treatment, these centers should use approved study protocols with informed consent and appropriate follow-up of patients, partners, and offspring.

INFERTILITY TREATMENT WHEN BOTH PARTNERS ARE HIV POSITIVE

As with any couple presenting for evaluation and treatment, both members of an HIV-infected couple may have normal fertility potential or one or both may have impaired fertility. If an HIV-infected couple asks for medical advice regarding pregnancy, they must be encouraged to adopt protocols that have been demonstrated to be safe and effective in Institutional Review Board (IRB)–approved research studies. Implementation of additional IRB-approved protocols for collection and publication of data on pregnancy and seroconversion outcomes is also encouraged. If the viral load can be suppressed to undetectable levels in both partners, the couple may be able to have a child who is free of HIV. Aggressive drug therapy with protease inhibitors and other antiretroviral therapy can extend life and improve health in HIV-infected persons; however, it is unknown whether or not they will ultimately have a normal or near-normal life expectancy. The child may lose one

or both parents to acquired immunodeficiency syndrome (AIDS) before he or she reaches adulthood, although recent success with combination antiretroviral therapy has significantly reduced death rates of infected persons.

ETHICAL ISSUES RAISED BY KNOWINGLY RISKING THE BIRTH OF A CHILD WITH HIV

The risk of HIV transmission to offspring when one or both parents are seropositive can be greatly reduced but not eliminated. This risk raises ethical issues concerning the scope of freedom to reproduce, what is considered to be harm sufficient to justify restricting that freedom, and the responsibilities of health care professionals faced with a request to provide services to HIV-infected patients.

Does a couple's desire to have genetic offspring justify the risk of transmitting a serious disease to their child? Although the risk can be reduced in many ways, and recent data show no instances of vertical transmission using sperm-prepared IUI or IVF with ICSI, theoretically the risk cannot be completely eliminated. Those who assess the ethics of assisting such patients to have children must address the question of whether offspring born with HIV are harmed despite the preventive steps taken. They must consider that some risk remains that the child will be born with HIV. Until sperm preparation techniques prove repeatedly and completely effective, there may be no way, short of refraining from reproduction altogether, to completely prevent some cases of HIV transmission. In situations in which a child could be born with a serious disease, one can argue that individuals are not acting unethically in proceeding with reproduction if they have taken all reasonable precautions to prevent disease transmission and are prepared to love and support the child, regardless of the child's medical condition. Similarly, one can argue that health care providers are not acting unethically if they have taken all reasonable precautions to limit the risk of transmitting HIV to offspring or to an uninfected partner. It would not, however, be ethically acceptable for a physician, clinic, or institution to proceed with reproductive assistance if they lacked the clinical and laboratory resources needed to effectively care for HIV-infected couples who wish to have a child. In such instances, the medical care provider should refer couples to a center that has these resources.

The ethical issues raised here are similar in some respects to those in couples who know that they are carriers of an autosomal recessive disease, such as Tay-Sachs disease, sickle-cell anemia, or cystic fibrosis. Such couples may choose to take the risk of having an affected child rather than use IVF plus preimplantation genetic diagnosis, which enables prospective parents to deselect embryos found to express certain genetic anomalies, forgo biologic parenthood, adopt, use a gamete donor, or, if a test result is positive, terminate the pregnancy. The risk of transmitting an autosomal recessive genetic disease through natural conception cannot be reduced below 25%, whereas the risk of HIV transmission can be reduced to a substantially lower number—in some cases, to <2%—when appropriate therapeutic measures are taken. Health care workers who are willing to provide reproductive assistance to couples whose offspring are irreducibly at risk for a serious genetic disease should find it ethically acceptable to treat HIV-infected individuals or couples who are willing to take reasonable steps to minimize the risks of transmission.

TESTING INFERTILE COUPLES FOR HIV

The Centers for Disease Control and Prevention estimate that approximately 200,000 persons in the United States have undiagnosed HIV (17). Because most of these persons are of reproductive age, the question arises of whether or not practitioners should require HIV testing for all couples seeking medical or surgical reproductive assistance. The American College of Obstetricians and Gynecologists recommends that obstetrician/gynecologists routinely screen their women patients aged 19–64 years for HIV regardless of individual risk factors (18).

In the case of gamete donors, testing for HIV and other sexually communicable diseases is ethically justified to protect the health of the gamete recipients. The Food and Drug Administration mandates that all anonymous and known directed gamete donors be screened for high-risk factors and undergo testing for HIV and other viral infections (19). The Centers for Disease Control and Prevention, the American Association of Tissue Banks, and the American Medical Association all strongly recommend HIV testing for every gamete donor. The ASRM practice guidelines recommend that all gamete donors and recipients be tested for HIV and other sexually transmitted diseases and that testing be offered also to the recipients' partners (20). Testing donors and recipients for potentially transmittable infectious conditions can be reassuring to all parties involved in ART and should be strongly encouraged.

It is especially important to test persons who are considered to be at high risk for HIV infection, such as those who have a history of repeated sexually transmitted diseases, multiple sexual partners without barrier protection, bisexual or homosexual behavior, or IV drug use. Knowing the HIV status of the at-risk individual or couple before establishment of a pregnancy could enable health care providers to better assist their patients in making safer reproductive choices.

It is ethically appropriate for practitioners to encourage HIV testing for all couples who want to have children, not just those who request infertility treatment. To mandate that people be tested solely because they request medical assistance in having a child would unreasonably infringe on their personal liberty and introduce an unjustifiable distinction between those who seek treatment for infertility and those who do not.

On the other hand, it may be appropriate to recommend HIV testing as good medical practice because there are effective means to significantly lessen the chance for HIV transmission to an uninfected partner and to offspring. An analogy is the common practice of recommending that women seeking to become pregnant be tested for rubella immunity because infection during pregnancy could cause serious birth defects in the offspring. For couples in which the man has unexplained obstructive azoospermia or congenital absence of one or both vasa deferentia, it is becoming standard practice to recommend testing for mutations of the cystic fibrosis transmembrane conductor gene to evaluate the risk of having a child with cystic fibrosis. Few people refuse these tests.

Couples should consider HIV testing as part of responsible parenting. Often associated with testing is the presumed stigma of some past sexual or drug-related misbehavior. Clinicians have a responsibility to educate their patients about the possible means by which infections can be acquired and the advantages of knowing the test results before a pregnancy is established.

HIV AND THE HEALTH PROFESSIONAL

Health professionals care for patients with serious and potentially contagious diseases, knowing that they themselves could become infected. Knowledge of diseases, combined with careful hygienic practices, has allowed caregivers to reduce that risk. In the late 1990s, the Centers for Disease Control and Prevention identified only 56 persons who had documented occupational transmission

of HIV and another 138 people with possible occupational transmission (21). Most were nurses and laboratory technicians who accidentally inoculated themselves with a patient's blood by a needle stick or were splashed with bloody fluid and had significant mucocutaneous exposure. None of these cases of HIV transmission occurred in the context of current ART (13).

If standard universal precautions to prevent infectious disease transmission are taken, the risk of virus transmission to medical caregivers is very small and, in itself, is not a sufficient reason to deny reproductive services to HIV-infected individuals and couples. Clinicians have the same obligation to care for those infected with HIV as to care for patients with other chronic diseases. Concern about the public's perception of a clinic or provider that cares for HIV-infected patients is insufficient cause to deny services.

Clinicians faced with requests for reproductive assistance from persons who are HIV infected should be aware of the 1998 United States Supreme Court decision in *Bragdon v. Abbott* (22). The Court ruled that a person with HIV is considered to be "disabled" and therefore protected under the Americans with Disabilities Act (23, 24). According to that decision, persons who are HIV infected are entitled to medical services unless a physician can demonstrate "by objective scientific evidence" that treatment would pose "a significant risk" of infection. The Court determined that having HIV was a disability because it interfered with the "major life activity" of reproduction, owing to the risk of transmitting HIV to offspring. Unless health care workers can show that they lack the skill and facilities to treat HIV-infected patients safely or that the patient refused reasonable testing and treatment, they may be legally, as well as ethically, obligated to provide requested reproductive assistance.

IMPROVING ACCESS TO CARE FOR HIV-INFECTED INDIVIDUALS

Despite improved outcomes in the use of IUI and IVF with ICSI to virtually eliminate the risk of vertical and horizontal transmission of HIV, access to these reproductive technologies for seropositive individuals is extremely limited. Fewer than 3% of U.S. ART practices registered with the Society for Assisted Reproductive Technologies provide service to couples in whom one or both partners are HIV infected (25). This lack of access is attributable to concerns about transmission to clinic personnel, fear of cross-contamination by gametes and embryos being cultured and stored on clinic premises, lack of expertise by clinicians in handling infectious patients and their gametes, and the high cost to clinics for providing separate laboratory space and equipment to minimize the risk of cross contamination, as recommended by ASRM (25).

To date, there have been no reported cases of occupational transmission to ART personnel or contamination of gametes or embryos in the clinic setting that would support denial of service to HIV-infected individuals or couples (13). The few centers that do provide care report seeing happy and grateful families, many of whom travel a great distance for access to the safest method of reproduction currently available. To the extent it is economically and technically feasible, ART providers should widen access to HIV-infected patients who desire to procreate in a manner that minimizes the risk of viral transmission to their partners and offspring (26, 27).

CONCLUSION

Human immunodeficiency virus infection is classified as a chronic disease. It is treatable, but not yet curable. Significant advances in HIV treatment appear to have delayed the onset of AIDS and its consequences in many, though not all, infected persons. The potential for HIV-infected persons to have uninfected children and not transmit the virus to their partners has been substantially enhanced, but success cannot be guaranteed. Health care providers and HIV-infected persons together share responsibility for the safety of the uninfected partner and potential offspring. When an affected couple requests assistance to have their own genetically related child, they are best advised to seek care at institutions with the facilities that can provide the most effective evaluation, treatment, and follow-up. Alternatively, they may be advised to look to other options and consider donor gametes, adoption, or not having children.

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