Recommendations for reducing the risk of viral transmission during fertility treatment with the use of autologous gametes: a committee opinion

Sexually transmitted infections are of major concern to reproductive specialists. Heading the list are human immunodeficiency virus types 1 and 2 and hepatitis B and C viruses. These pathogens, which may cause incurable chronic infections, can be transmitted through assisted reproductive technologies and from infected mothers to the fetus or newborn. This document replaces the document of the same name last published in 2013 (Fertil Steril 2013;99:340–6). (Fertil Steril 2020;114:1158–64. ©2020 by American Society for Reproductive Medicine.)

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SEXUALLY TRANSMITTED VIRUSES CAN CAUSE CHRONIC LIFELONG INFECTIONS

The past two decades of intensive virus research has provided cure strategies for hepatitis C (1), but not for human immunodeficiency virus (HIV) types 1 and 2 and hepatitis B virus (HBV). There is a substantial body of information on mechanisms and risk factors underlying sexually transmitted infection (STI), suggesting risk-reduction strategies for prevention of transmission. Sensitive and precise diagnostic tests allow the early detection and monitoring of viral infections, and new antiviral drugs make it possible to manage many chronic viral infections. HIV-infected individuals, in particular, are now living longer, healthier lives and, in ever increasing numbers, are choosing to have children.

The American Society for Reproductive Medicine (ASRM) has stated that fertility services cannot be withheld ethically from individuals with chronic viral infections, including HIV, if a center has the resources to provide care. Centers that do not have the resources or facilities to provide care should assist in referral to a center with protocols in place to manage such patients (2). The guidance in this document provides strategies, based on scientific principles and clinical experience, for reducing the risk of viral transmission in couples seeking fertility treatment. Recommendations are aimed at the following: 1) reducing viral load in an infected partner(s); 2) reducing exposure and susceptibility of a noninfected partner; and 3) promoting honest, detailed discussions with patients about available scientific evidence and risk-reduction strategies to provide a basis for informed consent. Some clinics in Europe and North America have incorporated these principles into practice with encouraging results (3, 4). The Centers for Disease Control and Prevention (CDC) has concluded that people with HIV who take antiretroviral therapy as prescribed and achieve and maintain an undetectable viral load have effectively no risk of transmitting HIV through sex (5).

EXISTING SCREENING/TESTING GUIDELINES

Sexually intimate partners are excluded from United States Food and Drug Administration–mandated screening and testing for viral infections (6). However, couples proceeding to assisted reproductive technologies (ART) are advised to undergo viral screening. Such screening can help to
ensure that appropriate precautions are taken to minimize risk of viral transmission to partners and offspring and allows for adequate segregation and storage of specimens to minimize the risk of cross-contamination. Intimate couples in which one or both partners are positive for HIV, HBV, or hepatitis C virus (HCV) should be treated by fertility centers that are equipped to care for such couples [2]. This document does not address all viral diseases as they are related to fertility care. For example, ASRM has specific recommendations regarding Zika infections and West Nile virus [7, 8].

**REQUIREMENTS FOR TREATMENT**

Couples in which one or both partners are infected with a sexually-transmissible pathogenic virus should receive in-depth preconceptional counseling on the risks of sexual and vertical transmission of their infections. In many cases, the viral infection can be effectively treated, so that risk of transmission in intercourse is eliminated. In cases where the viral infection cannot be effectively treated, or if the couple has the need for fertility treatments because of an infertility diagnosis (e.g., low sperm counts), ART may be required for conception.

Counseling and education concerning safe-sex practices during ART should be provided and emphasized. In cases where the male, but not the female, partner is infected, the couple should understand the merits of using condoms and adhering to antiviral therapy throughout fertility treatment, pregnancy, and the postpartum period. Serial diagnostic testing of the uninfected partner is recommended throughout treatment and pregnancy and for both mother and infant during the first year after birth. Informed consent should be explicit and as thorough as possible, emphasizing that the risk of transmission cannot be completely eliminated even when specific risk-reduction strategies are followed. In-depth psychologic, medical, and obstetrical care ideally should be provided by a multidisciplinary medical team that includes an expert in infectious disease.

**MANAGEMENT OF CRYOPRESERVED TISSUE**

Contamination with HIV, HBV, and HCV has been documented in ART clinics [9] and blood banks [10]. Although there is no documentation of cross-contamination of cryopreserved stored human tissue, it is highly recommended that samples from viral carriers be processed in a separate laboratory or designated space within the main laboratory. HIV, HCV, HBV, and possibly other viruses can survive in liquid nitrogen, making it possible to cross-contaminate samples in liquid nitrogen storage tanks, although this risk is very low. To protect cryopreserved specimens from the potential cross-contamination risk, it is advised that HIV-, HBV-, and HCV-infected specimens be stored in separate tanks. The following measures have been proposed to further reduce the risks of cross-contamination of samples in liquid nitrogen storage:

1. Use of specimen containers guaranteed by the manufacturer to withstand freezing temperatures and thawing cycles.
2. Use of a closed-system vitrification device or sealing techniques to prevent the direct contact of cryopreservation devices with liquid nitrogen.
3. Storage of samples in liquid nitrogen vapor instead of in the liquid phase of nitrogen itself. Recent studies have demonstrated that the use of liquid nitrogen vapor storage of both oocytes and sperm may be a viable alternative to storage of gametes and/or embryos in the liquid phase alone, which has the theoretical potential of becoming contaminated [11, 12] but may pose more risk to the integrity of the sample if storage conditions are compromised.
4. Use of sperm-wash techniques to decrease the viral load before freezing semen samples [13].

**SPERM-WASH METHODS**

Sperm-wash procedures involving density-gradient centrifugation followed by a sperm swim-up step have been used to separate motile sperm from free HIV virus and HIV-infected somatic cells [14–16]. Quantitative assessment of HIV in semen before and after the sperm-wash procedure indicates that >99% of HIV is removed [15]. Virologic testing of the sperm fraction for the presence of residual detectable HIV before its use for insemination can provide an added measure of safety, as up to 5%–10% of samples may contain residual virus after this procedure [16]. Similar sperm preparation techniques have been used to separate HCV from sperm [17] and may be useful for other viral infections where the majority of virus is found in free form or associated with somatic cells (i.e., white blood cells, epithelial cells). A method for limiting contamination of the sperm during the gradient separation is the double-tube method with the use of a product called Frohnert (Nidacon) [19]. This product is a second tube that serves as a channel to retrieve the sperm pellet without coming into contact with the gradient material along the sidewalls of the tube, which may be contaminated with leukocytes or free virus.

**VIRUS-SPECIFIC RISK REDUCTION STRATEGIES**

**Human Immunodeficiency Virus**

HIV-1 and HIV-2 are retroviruses that primarily infect T lymphocytes and other immune cells. HIV-1 and HIV-2 have the same modes of transmission and put women at risk of acquiring opportunistic infections and progressing to acquired immunodeficiency syndrome (AIDS). Infection with HIV-1 leads to AIDS and death in most individuals if left untreated. Immunodeficiency associated with HIV-2 infection may be less severe and develop more slowly.

HIV/AIDS is endemic in sub-Saharan Africa and Southeast Asia and is prevalent throughout the world in high-risk groups, including users of unscreened blood products, intravenous drug users, sex workers, and men who have sex with men. HIV is transmitted both sexually and vertically through blood, semen, vaginal secretions, and breast milk. The rate of HIV heterosexual transmission is relatively low (approximately 1 per 1,000 acts of unprotected intercourse) [18]. Risk factors for HIV transmission include genital-tract
infections and ulceration, sexual practices that induce trauma or bleeding, and lack of male circumcision (19).

The rate of HIV transmission is highly associated with peripheral blood viral load and is lowest in individuals with peripheral viral loads that are undetectable (20). HPTN 052, a phase 3 randomized trial, demonstrated that a 93% reduction of HIV transmission within serodiscordant couples (where one person is HIV infected and the other is not) if the HIV-infected partner was taking antiretroviral therapy (21). Ongoing research now supports the CDC statement that people with HIV who take antiretroviral therapy as prescribed and achieve and maintain an undetectable viral load have effectively no risk of transmitting HIV through sex (5, 22, 23).

The CDC estimated that 8 to 141 women were infected through donor insemination from 1980 to 1984 before stricter donor screening and semen quarantine practices were implemented (24). Because HIV is found primarily in white blood cells and as cell-free virions in semen (25), sperm-wash techniques that separate motile sperm from the round cell and seminal fluid fractions, including density-gradient centrifugation and swim-up methods, can markedly reduce HIV levels before insemination (15). Several European and North American fertility centers have used sperm-wash and other risk-reduction techniques for HIV-discordant couples desiring children. Since 1987, several thousand attempts at intrauterine insemination (IUI) and in vitro fertilization (IVF) have been reported in which processed sperm from HIV-seropositive men were used to achieve pregnancy in HIV-seronegative women without HIV infection occurring in uninformed partners or offspring (4, 26, 27). Risk-reduction techniques also have been used for couples where both partners are HIV infected to reduce the risk of superinfection of the female partner with different strains of HIV or drug-resistant HIV (23).

It is highly recommended that both partners should undergo a sexual health screen. Bacterial vaginosis and infections with herpes simplex virus type 2, Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoea, and Treponema pallidum can increase HIV-1 transmission (28) and should be treated. The use of condoms during sex should be recommended. Practices and behaviors that lacerate mucosal surfaces and other risk factors for HIV transmission should be avoided (29). Both partners should undergo a fertility assessment so that the number of exposures is minimized. Ovulation induction, IUI, or intracytoplasmic sperm injection (ICSI) should be applied as indicated based on any diagnosis of infertility.

HIV viremia should be minimized in the infected partner (peripheral blood viral load <40 copies/mL) through the use of highly active antiretroviral therapy to reduce levels of HIV in semen. If there is no diagnosis of infertility, the couple can attempt to conceive by means of intercourse. If IUI or IVF is needed, a sperm-wash protocol should be used to enrich motile sperm and to reduce or eliminate HIV-infected white blood cells and free virus in the fraction isolated for insemination. The most widely used sperm-wash procedure for HIV reduction involves the use of gradient centrifugation followed by a sperm swim-up procedure (14, 30). Trauma to the cervix or uterus during the IUI procedure must be minimized. A systemic review of 40 studies of 1,023 HIV-negative women undergoing 2,863 IUI or IVF/ICSI procedures with sperm from their HIV-positive partners revealed no cases of seroconversion in the woman and no infected infants (31). A second systematic review from 2016 showed no HIV transmission in 8,212 IUI cycles and 1,254 IVF cycles among HIV-discordant couples (32).

Approaches such as preexposure prophylaxis (PREP) with antiretroviral drugs (33–35) and locally applied vaginal estrogen gels (36) may further reduce the susceptibility of the uninfected female partner. PREP with the use of tenofovir and emtricitabine, rapidly acting antiretroviral drugs with long half-lives, are endorsed in serodiscordant couples as one option to protect the uninfected partner during conception and pregnancy (37).

The uninfected partner in a discordant couple should be tested for HIV at 3-month intervals during fertility treatments and pregnancy. The couple should use condoms and consider PREP. If HIV infection is detected in the female partner during pregnancy, she should be referred to an obstetrical service experienced in managing HIV-infected women. Use of antiretroviral drugs during pregnancy and/or labor, use of cesarean section, and avoidance of breastfeeding can reduce the risk of vertical transmission of HIV to <2% (38).

**Hepatitis B**

HBV, a double-stranded DNA virus, is a major cause of acute and chronic hepatitis, cirrhosis, and hepatocellular cancer. HBV is one of the most common infectious diseases in the world; it has been estimated that 350 million people worldwide are HBV carriers (39–41). HBV can be transmitted parenterally, sexually, vertically, and via other routes of mucosal exposure. Approximately 25% of regular sexual contacts of HBV-infected persons will become seropositive for HBV (40), and HBV has been transmitted through artificial insemination (41). Health care workers ran a high occupational risk of HBV infection before universal precautions and HBV immunization were introduced in the workplace. Universal safety precautions and vaccination with HBV vaccine, available since 1982, are the most effective ways to reduce the risk of HBV infection (42).

HBV-infected individuals run a high risk of coinfection or superinfection with hepatitis D virus (HDV), a circular replication-defective RNA virus that requires the presence of HBV for replication (43). Approximately 25% of chronic HBV carriers are coinfected with HDV, which increases their risk of cirrhosis from 15% to 80%. Vertical transmission of HDV has been documented. Because HBV is needed for HDV replication, measures to prevent the transmission of HBV, such as vaccination of uninfected partners and newborns, prevent the transmission of HDV.

All couples being evaluated for IVF should be screened for HBV via hepatitis B surface antigen (HBsAg). In couples who are discordant for HBV infection, the partner who is seronegative for HBsAg and has no evidence of immunity on additional serologic testing (i.e., is negative for hepatitis B surface antibody [HBsAb] and core antibody) should be vaccinated against HBV. Fertility treatments may be initiated once
the vaccinated partner’s anti-HBsAb titer is positive. Modified sperm-wash to reduce viral load is not required after the female partner is immunized against HBV.

All HBsAg-positive HBV-infected females should be offered referral to a hepatologist to determine if she is immune tolerant or has immune-active disease. Immune-tolerant individuals are a carrier of the virus with normal alanine transaminase and aspartate transaminase levels and do not have active hepatitis. Immune-active disease (previously termed chronic active hepatitis) occurs in those individuals who have elevated liver function tests associated with chronic hepatitis. For the immune-tolerant patient with HBV, the current recommendations would be to treat individuals with HBV DNA viral level >200,000 IU/mL with appropriate antiviral therapy. Treatment should be initiated at 28–32 weeks of gestation and continued up to 3 months postpartum. Patients with immune-active disease should be treated based on the usual recommendations for all nonpregnant women with appropriate antiviral therapy as determined by the hepatologist.

Cesarean section is not indicated owing to insufficient data to support its benefit in preventing vertical transmission. All infants born to HBsAg-positive mothers should receive immunoprophylaxis within 12 hours after birth. Immunoprophylaxis consists of both HBV vaccine and immunoglobulin, followed by two more injections of HBV vaccine in the first 6 months of life.

Breastfeeding is not contraindicated in women chronically infected with HBV (44). For mothers on antiviral therapy, the antivirals are minimally excreted in the breast milk and are an unlikely risk to the infant. It should be explained to the mothers that the actual risk is in fact unknown.

Hepatitis C

HCV is a blood-borne RNA virus that is transmitted primarily through parenteral exposure (blood products, shared needles, needle-stick injuries). HCV has also been detected in saliva, urine, semen, vaginal secretions, and breast milk, and sexual and vertical transmission are probable secondary modes of transmission (45). HCV infects 71 million individuals worldwide for a prevalence of >1%. In the United States, the prevalence is 0.8%–1.3%, but it is as high as 4.2%, for example, in the country of Georgia and 6.3% in Egypt (46). Most currently infected individuals in the United States are Baby Boomers born between 1945 and 1965, and most newly infected individuals are people who inject drugs (PWIDs) from 20 to 29 years of age. Currently, a large burden of chronic HCV infection in the United States is among PWIDS, individuals in jails and prisons, and men who have sex with men. HCV is a highly pathogenic virus: 80% of patients infected with HCV develop chronic liver disease, 35% develop cirrhosis, and 5% progress to hepatocellular carcinoma (47). Unlike HBV, there is no vaccine for HCV. Therefore, it is essential to use risk-reduction measures during assisted reproduction.

Current recommendations are to test all pregnant women at the onset of prenatal care. This recommendation is extended to include the testing of all male and female patients before IVF. There is a small but measurable risk of HCV transmission via semen. All patients with hepatitis C should be counseled about the risks of transmission to their partner, which is rare through sexual transmission, and to their children through vertical transmission (occurring in 4%–6%). They should be referred to an hepatitis specialist for discussion of potential treatment and cure. Current treatment of hepatitis C with direct-acting antiviral (DAA) therapy is 98% effective in achieving a sustained virologic response (SVR; i.e., a cure) with 8–12 weeks of treatment. An SVR is defined as a negative HCV RNA 12 weeks after treatment. With the ease, accessibility of insurance coverage, and short duration of therapy, it is recommended to treat all patients before IVF (48).

Although few women have been studied, there does not appear to be an increase in adverse pregnancy outcomes in HCV-infected pregnant women. The risk of vertical transmission is increased with coinfection of HIV (19.4% risk), in patients with a high viral load (i.e., ≥ 2.5 × 10⁶ IU/mL), and with invasive procedures (49). Cesarean section for delivery is not recommended to prevent vertical transmission, there is no vaccine available to treat infants born to HCV-infected women; and breastfeeding is considered to be safe in women who are chronic carriers of HCV (48).

Human T-Cell Lymphotropic Virus Types 1 and 2

Human T-cell lymphotropic virus (HTLV) types 1 and 2 appear to be ancient retroviruses of humans that establish permanent infections but have low potential to cause human disease (50). HTLV-1 infects primarily CD4 T cells and is the cause of adult T-cell leukemia (ATL) and HTLV-1–associated myelopathy (HAM), also known as spastic paraparesis. Only 1%–4% of infected individuals develop either ATL or HAM. HTLV-2 infects CD8 T cells. Although HTLV-2 has no proven connection to human disease, links to neurologic disorders are suspected. The distributions of HTLV-1 and HTLV-2 in the United States differ from elsewhere in the world and is quite low. Semen donors are screened for HTLV-1 and HTLV-2 because of the potential for transmission through ART procedures. Because HTLV-1 and HTLV-2 have several properties in common with HIV, risk-reduction protocols devised for HIV-discordant couples that separate infected white blood cells and free virus from sperm (i.e., sperm-wash before insemination) could be applied in cases where semen from directed donors infected with HTLV-1 or HTLV-2 is used to inseminate an uninfected partner.

SUMMARY

- Infertile couples should be advised that transmission of viral hepatitis and HIV in assisted reproduction is possible, but the magnitude of the risk is likely low for a low-risk population.
- People with HIV who take antiretroviral therapy as prescribed and achieve and maintain an undetectable viral load have effectively no risk of transmitting HIV through sex.
- Viral screening of intimate partners undergoing fertility treatment is not required, but it can help to ensure that
appropriate precautions are taken to greatly minimize risk of transmission to uninfected partners and offspring.

CONCLUSIONS

- Good clinical practice dictates that fertility services should not be withheld from individuals with chronic viral infections, including HIV, if the center has the necessary resources to provide care. Referral to a center having such capabilities is also appropriate.
- There is good evidence to support the recommendation that antiretroviral drugs should be used in the HIV-infected partner to reduce HIV viremia.
- While there is insufficient evidence to endorse the recommendation, best-practice guidelines recommend that semen and embryos from patients infected with HIV, HCV, or HBV should be stored in separate HIV-, HCV-, or HBV-designated cryostorage tanks owing to the theoretical risk of transmission.
- There is good evidence to support the recommendation, if the male partner is infected with HIV and ART is needed for an infertility diagnosis, that antiretroviral drugs should be used in the HIV-infected partner to reduce HIV viremia. Sperm-wash methods could be used to further reduce the levels of HIV-infected white blood cells and free virus in the insemination fraction of IUI specimens. In addition, strategies to avoid infection for the uninfected partner should include condom use as well as PREP.
- There is good evidence to support the recommendation that if one partner is infected with HBV, the seronegative partner should be vaccinated against HBV. Once the female partner has been immunized against HBV, sperm-wash alone should be used to reduce HBV viral load from the male partner is unnecessary.
- There is good evidence to support the recommendation that infants born to mothers who are HBV positive should receive both hepatitis B immunoglobulin and the hepatitis B vaccine within 12 hours after birth. Breastfeeding of newborns is not contraindicated.
- There is good evidence to support the recommendation that all men and women undergoing IVF be screened for HCV and that infected individuals be treated with DAA therapy. Infertility treatments should be delayed until SVR is achieved. There is good evidence to support the recommendation that women who are HCV infected should be counseled about the risk of transmission of HCV to their fetus with increasing viral loads and positive HIV status. Breastfeeding is not contraindicated.

Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the ASRM have approved this report.

This document was reviewed by ASRM members, and their input was considered in the preparation of the final document. The following members of the ASRM Practice Committee participated in the development of this document: Alan Penzias, M.D. (Chair), Ricardo Azziz, M.D., M.P.H., M.B.A., Kristin Benidikson, M.D., Tommaso Falcone, M.D., Karl Hansen, M.D., Ph.D., Micah Hill, D.O., William Hurt, M.D., M.P.H., Sangita Jindal, Ph.D., Suleena Kalra, M.D., M.S.C.E., Jennifer Mersereau, M.D., Catherine Racowsky, Ph.D., Robert Rebar, M.D., Richard Reindollar, M.D., Anne Steiner, M.D., M.P.H., Dale Stovall, M.D., Cigdem Tanrikut, M.D., Hugh Taylor, M.D., and Belinda Yaeger, M.D. The Practice Committee acknowledges the special contribution of Lisa Rahangale, M.D., M.P.H., Robert Reindollar, M.D., and Matthew (“Tex”) VerMilyea, Ph.D., in the preparation of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

REFERENCES


Recomendaciones para reducir el riesgo de transmisión viral durante el tratamiento de fertilidad con el uso de gametos autólogos: una opinión del comité.

Las infecciones de transmisión sexual son motivo de gran preocupación para los especialistas en reproducción. Encabezando la lista se encuentran los virus de inmunodeficiencia humana tipo 1 y 2 y los virus de la hepatitis B y C. Esos patógenos, los cuales pueden causar infecciones crónicas incurables, pueden ser transmitidos a través de técnicas de reproducción asistida y a través de madres infectadas al feto o al recién nacido. Este documento reemplaza al documento del mismo nombre publicado por última vez en 2013 (Fertil Steril 2013; 99: 340-6).