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REVIEW

Guidelines for risk reduction when handling gametes from infectious patients seeking assisted reproductive technologies

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Abstract According to the Americans with Disabilities Act (1990), couples with blood-borne viruses that lead to infectious disease cannot be denied fertility treatment as long as the direct threat to the health and safety of others can be reduced or eliminated by a modification of policies or procedures. Three types of infectious patients are commonly discussed in the context of fertility treatment: those with human immunodeficiency virus (HIV), hepatitis C or hepatitis B. Seventy-five per cent of hepatitis C or HIV positive men and women are in their reproductive years, and these couples look to assisted reproductive techniques for risk reduction in conceiving a pregnancy. In many cases, only one partner is infected. Legal and ethical questions about treatment of infectious patients aside, the question most asked by clinical embryologists and andrologists is: "What are the laboratory protocols for working with gametes and embryos from patients with infectious disease?" The serostatus of each patient is the key that informs appropriate treatments. This guidance document describes protocols for handling gametes from seroconcordant and serodiscordant couples with infectious disease. With minor modifications, infectious patients with stable disease status and undetectable or low viral load can be accommodated in the IVF laboratory.

KEYWORDS: hepatitis C, hepatitis B, HIV, IVF, sperm purification, standard precautions

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Introduction

Around 4.2 million people of childbearing age in the USA are infected with HIV, hepatitis C (HCV), hepatitis B (HBV), or a combination. For those seeking assisted reproductive techniques, laboratory protocols can be developed to safely accommodate virus-positive patients. These protocols will reduce the risk of infection to the staff, to the patients themselves and to other patients. The main risk to clinical staff is through needle punctures and splash or aerosol exposures. The risk to laboratory staff may come at the time of oocyte retrieval when blood products are introduced into the laboratory; at the time of semen processing; at the time of in-vitro insemination; during culture of gametes and embryos; and at the time of cryopreservation of oocytes, embryos or sperm. Patients may be exposed to risk if protocols are not in place to prevent cross-contamination of samples or if protocols are not strictly followed. Unsafe procedures include improper labelling of containers, inadequate sanitation between patients, improper handling of body fluids and use of blood products contaminated with infective agents.

Control of disease transmission requires a team management approach. It is critical to have open communication among the laboratory and clinical staff about protocols, testing, tests results, precautions and care offered to the patient. It is essential that universal or standard precautions be observed at all times. That is, all tissues and cells should be handled as if they are from an infectious patient. Each fertility programme should determine its comfort level with handling gametes from infectious patients. These patients are entitled to fertility options, so caution and appropriate modification on the part of the laboratory staff is required whenever possible. In this guideline, handling gametes and embryos from patients with HIV, HBV and HCV will be discussed (**Table 1**).

Published guidelines

Published guidelines on laboratory safety when handling gametes from infected patients are limited and do not offer comprehensive hands-on recommendations for laboratory staff (Clarke, 1999; Gilling-Smith et al., 2005; Practice Committee of American Society for Reproductive Medicine, 2013).

Table 1 Blood-borne viruses that can be sexually transmitted and are routinely screened in fertility couples.

Name of virus	*Virus type and target*
Human immunodeficiency virus types 1 and 2	Retrovirus primarily infects helper T-cells (CD4) causing immunodeficiency syndrome.
Hepatitis C virus	RNA virus infects liver cells.
Hepatitis B virus	Double-stranded DNA virus infects liver cells.
Human T-lymphotrophic virus I and II	Retrovirus primarily infects CD4 T-cells causing adult T-cell leukaemia and myelopathy.
Cytomegalovirus	Herpes virus threatens immunocompromised individuals and is leading cause of congenital infection.

The European Society of Human Reproduction and Embryology Committee of the Special Interest Group on Embryology published guidelines for good practice in IVF laboratories (Magli *et al*, 2008), recommending treatment of patients infected with HIV, HBV or HCV using dedicated laboratory space at allocated times, and processing within a biosafety cabinet to prevent cross-contamination of patient specimens.

The Practice Committee of American Society for Reproductive Medicine (ASRM) (2013) recently issued guidelines for treating patients with infectious disease. These guidelines advise counselling, education and informed consent, and provide standards for screening sperm and egg donors. The ASRM also recommends separation in time or space, separate frozen storage and special sperm washing with viral check before freezing, if possible.

The United States Food and Drug Administration regulates third-party reproductive tissues, including sperm, oocytes and embryos as products for transplantation. Regulations include donor screening for infectious diseases, as well as quarantine, storage and labelling requirements.

The Human Fertilization and Embryology Act of the UK mandates separate frozen storage for sperm, oocytes and embryos for which the source patient tests positive for infectious disease. Heat-sealed cryopreservation straws are used by most European IVF centres treating HIV and HBV and HCV positive patients with no reported cases of cross-contamination (Clarke, 1999).

HIV infection

In the case of HIV, no vaccine is available (Mascola, 2015). The HIV virus uses reverse transcriptase to transcribe RNA into DNA (Schnittman and Fauci, 1994). Once the virus binds to the cell surface, commonly that of the helper T-cell ($CD4^+$) of the immune system, and fuses with the cell, the viral RNA is reverse transcribed into DNA that combines with the host cell DNA. Some infected $CD4^+$ cells in lymphoid tissues destroy themselves, leading to falling $CD4^+$ counts over time (Doitsh et al., 2014; Monroe et al., 2014). When the serum $CD4^+$ count falls below 200 per mm^3 (or about a drop of blood), HIV infection can become acquired immunodeficiency syndrome. The lymph nodes are infected by HIV, which travels into the blood to gain entrance to other body fluids, such as semen and breast milk (Schnittman and Fauci, 1994). HIV is typically detected in the serum, and the viral load is expressed as viral RNA copies per ml of serum, measured by polymerase chain reaction (PCR) assay (Hart et al., 1988).

Is HIV associated with the sperm cell?

Although many are convinced that HIV is not associated with sperm cells selected by gradient separation (Anderson et al., 2010; Gilling-Smith et al., 2006; Le Tortorec and Dejucq-Rainsford, 2010), controversy remains. Convincing evidence was published by Quayle et al. (1997; 1998) reporting no association of HIV with motile sperm collected by gradient