Journal of Reproductive Immunology 100 (2013) 20–29

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jreprimm

# Sperm viral infection and male infertility: focus on HBV, HCV, HIV, HPV, HSV, HCMV, and AAV

Andrea Garolla[a], Damiano Pizzol[a], Alessandro Bertoldo[a], Massimo Menegazzo[a], Luisa Barzon[b], Carlo Foresta[a,*]

[a] Department of Molecular Medicine, Section of Clinical Pathology & Unit for Human Reproduction Pathology, University of Padova, Via Gabelli 63, 35121, Padova, Italy
[b] Department of Molecular Medicine, Section of Microbiology and Medical Biotechnologies, University of Padova, Italy

ARTICLE INFO

*Article history:*
Received 17 October 2012
Received in revised form 20 March 2013
Accepted 20 March 2013

*Keywords:*
Ejaculate alteration
Male infertility
Sperm infection
Sperm parameters
Urogenital infections
Viral sexually transmitted disease

ABSTRACT

Chronic viral infections can infect sperm and are considered a risk factor in male infertility. Recent studies have shown that the presence of HIV, HBV or HCV in semen impairs sperm parameters, DNA integrity, and in particular reduces forward motility. In contrast, very little is known about semen infection with human papillomaviruses (HPV), herpesviruses (HSV), cytomegalovirus (HCMV), and adeno-associated virus (AAV). At present, EU directives for the viral screening of couples undergoing assisted reproduction techniques require only the evaluation of HIV, HBV, and HCV. However, growing evidence suggests that HPV, HSV, and HCMV might play a major role in male infertility and it has been demonstrated that HPV semen infection has a negative influence on sperm parameters, fertilization, and the abortion rate. Besides the risk of horizontal or vertical transmission, the negative impact of any viral sperm infection on male reproductive function seems to be dramatic. In addition, treatment with antiviral and antiretroviral therapies may further affect sperm parameters. In this review we attempted to focus on the interactions between defined sperm viral infections and their association with male fertility disorders. All viruses considered in this article have a potentially negative effect on male reproductive function and dangerous infections can be transmitted to partners and newborns. In light of this evidence, we suggest performing targeted sperm washing procedures for each sperm infection and to strongly consider screening male patients seeking fertility for HPV, HSV, and HCMV, both to avoid viral transmission and to improve assisted or even spontaneous fertility outcome.


## 1. Introduction

Sexually transmitted diseases (STDs) represent major health, social, and economic problems worldwide. Despite the discovery of antibiotics and vaccines, and the development of disease prevention and control programs, STDs remain a significant cause of acute and chronic diseases with possible involvement in pregnancy complications and infertility (Ochsendorf, 2008). In 1993 the World Health Organization (WHO) established the role of genital tract infections in human infertility (WHO, 1993). Most male genital tract infections may induce infertility and previous studies reported that 15–20% of infertile subjects are affected by semen infection (Weidner et al., 1999). Back in 2001, Dejucq and Jégou (2001) stressed the need to study and understand the role of viruses in fertility and since then progress has been made in this direction. Based on different sites of infection, various pathogenic mechanisms have been described:

(a) Systemic acute or chronic infections can result in transient or permanent infertility, impairing hormones,

* Corresponding author. Tel.: +39 049 8218517; fax: +39 049 8218520.
*E-mail address:* carlo.foresta@unipd.it (C. Foresta).

0165-0378/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jri.2013.03.004

testicular function, and spermatogenesis (La Vignera et al., 2011).
(b) Testicular involvement by orchitis directly impairs sperm production (Weidner et al., 1999).
(c) Male accessory gland (epididymis, prostate, and seminal vesicles) and urethral infections have been identified as playing a negative role in male reproductive function and fertility owing to obstruction or sub-obstruction, altered secretory function, and release of inflammatory mediators (La Vignera et al., 2011).

Semen infections are frequently present even in asymptomatic males, and they are often associated with poor sperm quality (Bezold et al., 2007). Moreover, seminal leucocytes can be indicators of male genital tract infection, but they can be completely lacking when a high load of infectious agents are present. Actually, the relevance of chronic viral infections as an etiologic factor of male infertility is believed to be underestimated (La Vignera et al., 2011). Heading the list of chronic viral sperm infections are: human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV) viruses. In particular, HIV infection has been demonstrated to be significant for chronic low genitourinary tract inflammation, sperm infection, and reduced fertility (Cardona-Maya et al., 2011). Recent studies have shown that the presence of HBV or HCV in semen adversely affects sperm parameters and in particular reduces forward motility (Lorusso et al., 2010). Furthermore, viral semen infection has been associated with an increased frequency of sperm aneuploidy and DNA fragmentation (Moretti et al., 2008). Little is known about HPV semen infection; however, growing evidence suggests that this virus might play a major role in male infertility (Perino et al., 2011). In fact, HPV has been recently demonstrated to have a negative influence on sperm parameters, the fertilization process and the abortion rate (Foresta et al., 2010a,b, 2011a; Pérez-Andino et al., 2009; Perino et al., 2011). Other common sexually transmitted viruses able to colonize semen and thus of major concern for reproductive specialists are herpesviruses (HSV), human cytomegalovirus (HCMV), and adeno-associated virus (AAV). At present, EU directives for the viral screening of couples undergoing assisted reproduction techniques (ART) require evaluation of HIV, HBV, and HCV (Wingfield and Cottell, 2010). Besides the risk of horizontal or vertical transmission to a partner or neonate (Englert et al., 2004), the impact of viruses on male reproductive function concerns in particular the ability of these infections to induce an impairment of general health and thereafter infertility. Furthermore, both the possible presence of viral DNA or RNA at the sperm level and the treatment of patients with antiviral and antiretroviral therapies able to induce testicular damage may have a further detrimental effect on sperm parameters (Lorusso et al., 2010). This review attempts to focus on the interactions between defined sperm viral infections and their association with male fertility disorders. Data were acquired by a study of medical literature using the following search terms: ejaculate alteration, male infertility, sperm infection, sperm parameters, urogenital infections, and viral sexually transmitted disease.

## 2. HBV sperm infection

During HBV infection, the virus can be found in many secretions, semen, and other tissues beyond the liver and blood. HBV is not only able to pass through the blood–testis barrier and enter the male germ cells, but also integrate into their genomes. Several methods have been developed for the detection of HBV DNA in semen. Qian et al. (2005) successfully used quantitative real-time PCR to investigate the viral load in the semen of HBV-infected patients who were seeking assisted reproduction. Using fluorescence in situ hybridization (FISH) Huang et al. (2003) showed that HBV DNA can be integrated into the sperm chromosomes of HBV carriers and may be vertically transmissible via the germ cells. Moreover, they demonstrated that HBV infection may have mutagenic effects on sperm chromosomes, which are nonspecific and multi-sited, leading to genome instability. This finding suggested that HBV sperm infection can produce hereditary effects, inducing chromosome aberrations.

### 2.1. HBV sperm infection and male fertility

Regarding the impact of HBV on seminal parameters, it is well known that HBV infection may cause male infertility by damaging spermatozoa (Table 1). Lorusso et al. (2010) found that sperm concentration, motility, morphology, and viability were significantly impaired in HBV-seropositive patients. Other studies showed that subjects with HBV chronic infection had alteration of sperm parameters (Moretti et al., 2008; Vicari et al., 2006) and in particular a trend toward a negative correlation with the viral load was found. By in vitro studies, Kang et al. (2012) demonstrated that co-incubation of human spermatozoa with hepatitis B virus S protein induced a loss of sperm mitochondrial membrane potential, thus reducing sperm motility. Moreover, they showed that HBs exposure induced oxidative stress in sperm cells up to the stage of apoptosis, as revealed by phosphatidylserine externalization, caspase activation, and DNA fragmentation. In view of these results, it is possible to conclude that HBV-infected males have a significantly impaired sperm quality compared with that of control men.

### 2.2. HBV sperm infection and assisted reproduction

Contamination of patients during artificial insemination has been described for HBV over the last 20 years (Englert et al., 2004). In vitro studies showed that when zona-free hamster oocytes were inseminated using human sperm carrying an HBV DNA plasmid, HBV genes were able to replicate and be expressed in two-cell embryos (Ali et al., 2006). These results suggest that human sperm cells might integrate the HBV DNA, acting as vectors for the transmission of HBV genes during IVF as well as ICSI procedures. Moreover, Zhou et al. (2011) recently reported that HBV infection, besides its association with poor sperm parameters, is associated with poorer ICSI and embryo transfer outcomes. In contrast, Lee et al. (2010) reported no adverse effect of HBV infection on the assisted reproduction results. Although in assisted reproduction, HBV