Zika virus infection in semen: effect on human reproduction

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Unique among vector-borne flaviviruses, Zika virus can infect testis and male genital tract, can persist in semen for months after symptoms onset, and be sexually transmitted.[1, 2, 3] In *The Lancet Infectious Diseases*, Guillaume Joguet[4] and colleagues report alterations of sperm and testicular function in men with Zika virus infection, with potential effect on human reproduction. In this prospective longitudinal study, the authors detected viral RNA in the semen of 11 of 15 tested men, including five with persistent seminal shedding after viral clearance in blood. Notably, they were able to isolate infectious virus from motile spermatozoa obtained using semen separation methods that are generally used in assisted reproductive procedures. Semen alterations were observed, including a decreased sperm count and a concurrent increment of multiple sperm anomalies, especially in patients with Zika virus RNA-positive seminal specimens, while recovery was observed at day 120 post infection. In addition, inhibin β concentrations decreased after infection, suggesting an impairment of Sertoli cells, which are key components of the blood–testis barrier, produce immunoregulatory factors, and provide support to sperm cells during spermatogenesis. These findings suggest a direct effect of viral infection on the testis or epididymis with impairment of sperm development, in agreement with findings in animal models.

In mouse models of Zika virus infection, the virus infects testicular stem-like peritubular myoid cells, spermatogonia, Sertoli cells, and epithelial cells of the epididymis, leading to inflammation, massive cell necrosis, and testicular atrophy.[5, 6] In infected mice, sperm fragmentation and decreased sperm motility and count have been noted,[5, 6, 7] as well as a reduced rate of pregnancies and viable fetuses from females mated with Zika virus-infected males.[6] Like in mice, persistent Zika virus shedding in semen occurs in non-human primates, but the virus is detectable in the prostate and seminal vesicles, as well as in testes and epididymis.[8]

The reservoir of Zika virus infection in human genital tract is unknown. Localisation of Zika virus antigen by immunostaining in the head of mature spermatozoa of a patient with persistent Zika virus-positivity in semen[9] indicates that, like in animal models, spermatogonia are probably the main target of Zika virus infection. Seminal vesicles and prostate are also possible sites of viral replication and persistence, as suggested by isolation of infectious Zika virus in the semen of vasectomised men.[10, 11] As with other viral infections,[12] it is also conceivable that several pathogenic mechanisms might lead to impaired sperm production in patients with acute Zika virus infection—ie, systemic acute infection, which can alter hormones, testicular function, and spermatogenesis; testicular involvement, which directly impairs sperm production; and infection of male accessory glands and urethra, which might cause obstruction, altered secretory function, and release of inflammatory mediators.

Shedding of Zika virus in semen occurs in more than 50% of men with symptomatic infection, half of whom are long-term shedders, with viral RNA detectable in semen for months after viral clearance from blood.[1, 2, 3, 4] However, the presence of viral RNA does not entail active replication and infectivity. Available data indicate that infectivity is low after the first 2–3 months post infection, because, so far, isolation of replication-competent virus from semen and male-to-female sexual transmission have been reported up to 69 days and 41 days after symptoms onset, respectively.[11, 13] Based on these data, the current WHO guidance for the prevention of sexual transmission of Zika virus recommends abstinence or safe sexual practices for a 6-months period after potential exposure to the virus. The same timing recommendations are applied to the use of

semen within couples undergoing fertility treatment and to gamete donations. In this regard, Joguet and colleagues[4] show that sperm preparation procedures, which are used in assisted reproductive technology to reduce the risk of HIV and hepatitis C virus infection,[12] are not effective for Zika virus.

Notwithstanding the major recent advances in our knowledge of Zika virus biology and diseases, achieved especially with in vitro and animal studies, several questions on the effect of Zika virus infection on human health remain open. Studies such as that of Joguet and colleagues,[4] although with the limitations of a small patient population and absence of a control group, provide novel and valuable baseline information that warrant further research on the consequences of Zika virus infection on human reproduction. For example, studies are needed to identify the cells and compartments in male genital tract that are targeted by Zika virus infection, the reservoir of viral persistence in semen, the maximal duration of Zika virus infectivity of semen and risk of sexual transmission, and the long-term impact of infection on fertility.

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