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Commentary

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Monkeypox and Male Fertility: Is There Any Looming Danger?

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The current emergence of monkeypox virus infection, mainly reported from previously non-endemic regions, raised concerns about its transmission and possible implication on general health and wellbeing. The concern is spawned from the fact that the virus keeps spreading, and as of the 8 th September 2022, at least 88 countries have reported over 54191 cases globally (1). In the wake of the Covid-19 pandemic, this recent outbreak is mustering up thoughts of public panic, social disruption, severe illness, and comorbidities, including risks to fertility and offspring.

Monkeypox virus is an enveloped linear double-stranded DNA virus that belongs to the Orthopoxvirus genus of the Poxviridae family. This genus also comprises viruses like horsepox virus, Uasin Gishu virus, camelpox virus, cowpox virus, ectromelia virus, raccoonpox virus, skunkpox virus, taterapox virus, vaccinia virus, variola virus, volepox virus, abatino macacapox virus, akhmeta virus, and alaskapox virus.

Monkeypox is a zoonotic viral disease transmitted to humans from animals with symptoms similar to those seen in smallpox patients, although it is clinically less severe. It was first discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of monkeys kept for research. The first human case of monkeypox was recorded in 1970 in the Democratic Republic of the Congo during a period of intensified effort to eliminate smallpox. Monkeypox primarily occurs in Central and West Africa, often near tropical rainforests (2, 3).

The viral replication of the monkeypox virus occurs in the cytoplasm. This virus enters the host cell by attaching viral proteins to the host plasma membrane glycosaminoglycans, which then mediate cellular endocytosis of the virus. The fusion of the viral proteins with the host cell plasma membrane causes the virus to release its viral core into the host cytoplasm. This process leads to an expression of intermediate genes, which will enhance genomic DNA replication by the viral DNA polymerase. Once replication begins, the production of genes and subsequently viral structural proteins continues, which enhances the maturation of virus particles into brick-shaped intracellular mature virions. These virions are either released upon cell lysis or can acquire a second membrane from the Golgi apparatus and bud as extracellular virions through transportation via microtubules (2).

Therefore, the monkeypox virus can be transmitted through contact with the virus from an infected animal, virus-contaminated material, or infected person via body fluids (including vertical transmission), sores, respiratory droplets, respiratory secretions, skin lesions or plausibly through semen and vaginal fluids (2, 4).

While close physical contact is a well-known risk factor for transmission, it is unclear if monkeypox can be explicitly transmitted through sexual activities. Out of the available studies reporting monkeypox infection, seven articles (Table 1) have shown the presence of the virus in human semen (5-11). However, it is still unclear if the

Table 1. List of studies reporting the presence of monkeypox virus in the semen

Reference	Country	Number of patients tested	Number of positive patients	Plausible mode of transmission
[7]	Italy	1	1	Other route
[6]	Germany	2	2	Unprotected sexual intercourse
[5]	Italy	3	3	Unprotected sexual intercourse
[8]	Spain	9	7	Unprotected sexual intercourse
[9]	International case series	32	29	Unprotected sexual intercourse
[10]	Italy	1	1	Unprotected sexual intercourse
[11]	Canada	1	1	Unprotected sexual intercourse

presence of the virus in the semen led to transfection during intercourse or whether it is only related to close contact.

Of interest is the study of Antinori et al, who reported the presence of human monkeypox virus in the seminal plasma of three of four Italian men evaluated. It was shown that these men had unprotected sexual intercourse with multiple partners during the first two weeks of May 2022 and were admitted to two different hospitals between 17 and 22 of May 2022. The semen samples were collected 5-7 days before onset of symptoms, and these samples were positive for the monkeypox virus, with a quantification cycle (Cq) value ranging from 27-30. Although the correlation between Cq value and infectious viral load of monkeypox virus is not yet known, the results showed possible viral shedding in the semen (5). Similar results were displayed in one Italian patient living in Portugal, with a Cq value of 31 (7). Another study reported that out of nine semen samples analyzed from monkeypox virus infected patients, seven were positive for monkeypox virus as early as day four from symptom onset with Cq values ranging from 25.5 to 40 across different days (8). Similarly, the semen sample of a man from Canada was positive for monkeypox virus on day ten after onset of symptom (11). Lapa et al. reported that the semen sample of an Italian man was positive for monkeypox virus from day five after symptom onset until day nineteen with a Cq range of 27.8 to 40.6. The viral DNA was isolated from the semen on day six after symptom onset and inoculated in Vero E6 cells. After 48 *hr* of inoculation, evident cytopathic features were observed in the cells until end of experiment (96 *hr*). This suggests that prolonged shedding of monkeypox virus DNA can occur in the semen of infected patients for weeks after symptoms onset and semen collected in the acute phase of infection (day 6 after symptom onset) might contain a replication-competent virus and hence represent a potential source of infection. Therefore, it was concluded that transmission of monkeypox virus during sexual activity might be a viable and recognized route (10).

Additionally, Noe et al. reported that the semen samples of two German men who had unprotected sexual intercourse were positive for the monkeypox virus, with viral DNA concentrations comparable to blood (6). Recently, a group of clinicians retrospectively analyzed 528 cases of monkeypox infection diagnosed between April 27 and June 24, 2022, at 43 sites in 16 countries. They reported that 98% of the infected individuals were homosexual or bisexual men (median age was 38 years) and transmission was suspected to have occurred through sexual activity in 95% of these cases. In this study, monkeypox virus DNA was also detected in 29 of 32 semen samples analyzed (9).

On the other hand, four additional studies from Australia, Portugal, Romania, and USA showed that men (27, 1, 1 and 1, respectively) who also had a history of risky sexual behavior (*e.g.* unprotected sexual intercourse) displayed viremia; however, their semen samples were not tested (12-15). The presence of the monkeypox virus in the semen could be just a consequence of the viremia, because the inflammation caused by the viral infection could alter the blood-testis barriers and allow the virus to enter the testes (5).

The question remains if the presence of monkeypox in the seminal plasma would adversely affect overall male fecundity, either during or after monkeypox virus infection. Additionally, it is unclear whether this viral shedding causes trans-

mission through the semen, knowing that semen as the potential route of transmission has been proposed for other viral infections that were previously considered unlikely to be transferred sexually, including Ebola virus, Zika virus, and SARs-CoV-2.

There is evidence of the relationship between viral infection with members of the orthopoxvirus genus and orchitis in both humans and rodents. Of particular interest is the study of Phadke et al. who reported that infertile patients with smallpox infection had a higher incidence of azoospermia (42.57%) when compared to the control (17.87%), and that these patients with smallpox infection commonly presented with obstructive azoospermia (79.36%) (16). In patients with non-obstructive azoospermia, testicular lesions such as partial or complete arrest of spermatogenesis at various levels, germinal cell aplasia, severe tubular atrophy, and hyalinization of the tubules were encountered. However, whether the virus is present in the testicular epithelium, or whether the infection aggravated the infertility condition remains a matter of debate, because these patients were infertile even before contracting the smallpox infection. Additionally, studies have shown that men infected with SARS-CoV-2 displayed abnormal semen parameters, altered hormone profile, and disrupted spermatogenesis (17, 18). Furthermore, in 2017, 27 viruses were reported in semen, several of which were found to be involved in sexual transmission (19). In addition, during the last five years, the number of reports about viruses being present in the semen has increased such as monkeypox, Dengue virus, and Chapare virus, and undoubtedly this will negatively impact human fertility since the infection of the semen with other viruses has been shown to pose a danger to male fertility potential (20).

The available findings cannot be used to substantiate whether infection with monkeypox virus could harm male fertility potential. Therefore, it is recommended that the generic guidance on viral infections be strongly considered and adhered to, until position statements are made. Additionally, prospective parents, assisted reproductive technology (ART) patients, gamete donors and gestational carriers, who meet the diagnostic criteria for viral infection should avoid becoming pregnant or participating in any fertility programs until there is a certainty regarding the effect of monkeypox virus infection on male fertility potential and on future offspring.

Finally, it is advised that suitable precautions should be taken when engaging in sexual activities to minimize the potential risk of spreading and/or contracting monkeypox.

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Conflict of Interest

Authors declare no conflict of interest.

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