Potential mechanisms of intrauterine transmission of monkeypox virus

As the present outbreak continues to expand through sustained human-to-human transmission and due to a vaccine shortage, there is a strong possibility of monkeypox becoming globally endemic. The obstetric concern is the risk of vertical transmission of the monkeypox virus to the fetus. To date, at least 12 pregnant individuals with monkeypox have been identified: eight women (probably clade IIb) infected in 2022,[1,2] and four women (probably clade I) infected between 2007 and 2011.[3]

Monkeypox viral DNA within fetal and placental lesions has been detected concurrently at birth with real-time PCR. Placental histology from pregnancies with congenital cowpox and smallpox—orthopoxviruses closely related to the monkeypox virus—has also shown intracytoplasmic inclusions, known as Guarnieri bodies, within the decidua and viral cytopathic effects—such as granulomas, inflammatory infiltrate, and necrotic placental villi.[4,5] The findings support the potential for orthopoxviruses to breach the placenta, although the exact mechanisms remain uncharacterised.

We propose four pathways through which monkeypox could be vertically transmitted in utero (appendix).

First, monkeypox virus could ascend from the vagina and cervix to colonise cells in the chorionic membranes, including epithelial and mesenchymal cells and trophoblasts. Transmission via genital fluids is possible given the detection of replication-competent monkeypox virus from semen and prolonged viral DNA shedding in the reproductive tract. In miscarriages due to human cowpox, infectious virus is present within vaginal secretions, and cytopathic effects can be observed in the vagina and placenta for 4–6 weeks after maternal infection.[4]

Second, viraemia might allow monkeypox virus to reach the placenta through the spiral arteries in the uterus. From there, the virus could sequentially infect the decidua, extravillous trophoblast, or the placental villi to enter the fetal circulation. In congenital cytomegalovirus infection, apolipoprotein B messenger RNA–editing catalytic polypeptide-like 3 enzymes restrict viral replication in the decidua but not within the villi.[6] Because the same enzyme complex drives genetic changes in monkeypox clade IIb, the virus could evolve to target the placental perivascular cells preferentially during maternal viraemia.

Third, similarly to extracellular enveloped vaccinia virus, monkeypox virus might directly infect the syncytiotrophoblast by transcytosis or fusion with the trophoblast membrane.

Finally, inflammation associated with monkeypox virus could allow viral invasion of fetal blood. Innate and adaptive maternal immune responses by dendritic cells, natural killer cells, and T-lymphocytes in the decidua might release cytokines which disrupt the cortical actin network overlying the syncytiotrophoblast. Type 1 interferon responses induced by monkeypox virus could also contribute, as the release of IFNα or IFNβ antiviral mediators has been shown to damage human placental tissue ex vivo.

We declare no competing interests.

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1 Government of Brazil. Monkeypox epidemiological bulletin no 8 (emergency operations center). 2022. https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/variola-dos-macacos/boletim-epidemiologico-de-monkeypox-no-8-coe/view (accessed Aug 26, 2022).

2 Infectious Disease Society of America. Monkeypox: updates on testing, vaccination & treatment. https://www.idsociety.org/multimedia/clinician-calls/cdcidsa-monkeypox-updates-on-testing-vaccination--treatment/ (accessed Aug 26, 2022).

3 Mbala PK, Huggins JW, Riu-Rovira, T. Maternal and fetal outcomes among pregnant women with human monkeypox infection in the Democratic Republic of Congo. *J Infect Dis* 2017; **216:** 824–28.

4 Ferrier A, Frenois-Veyrat G, Schvoerer E, et al. Fatal cowpox virus infection in human fetus, France, 2017. *Emerg Infect Dis* 2021; **27:** 2570–77.

5 Garcia AGP. Fetal infection in chickenpox and alastrim with histopathologic study of the placenta. Pediatrics 1963; **32:** 895–901.

6 Megli CJ, Coyne CB. Infections at the maternal–fetal interface: an overview of pathogenesis and defence. *Nat Rev Microbiol* 2022; **20:** 67–82

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