MONKEYPOX AND PREGNANCY: FORECASTING THE RISKS

Pradip Dashraath, Karin Nielsen-Saines, Anne Rimoin, Citra Mattar, Alice Panchaud, David Baud

PII: S0002-9378(22)00651-2

DOI: https://doi.org/10.1016/j.ajog.2022.08.017

Reference: YMOB 14681

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 11 July 2022

Revised Date: 11 August 2022

Accepted Date: 11 August 2022

Please cite this article as: Dashraath P, Nielsen-Saines K, Rimoin A, Mattar C, Panchaud A, Baud D, MONKEYPOX AND PREGNANCY: FORECASTING THE RISKS, *American Journal of Obstetrics and Gynecology* (2022), doi: https://doi.org/10.1016/j.ajog.2022.08.017.

MONKEYPOX AND PREGNANCY: FORECASTING THE RISKS

Pradip Dashraath[1,2], Karin Nielsen-Saines[3], Anne Rimoin[4,5], Citra Mattar[1,2], Alice Panchaud[6], David Baud[7]

1. Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, National University Hospital, Singapore
2. Yong Loo Lin School of Medicine, National University of Singapore, Singapore
3. Division of Pediatric Infectious Diseases, Department of Pediatrics, David Geffen School of Medicine, UCLA, USA
4. Fielding School of Public Health, David Geffen School of Medicine, UCLA, USA
5. UCLA-Democratic Republic of the Congo (DRC) Health Research and Training Program
6. Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
7. Materno-fetal and Obstetrics Research Unit, Department Woman-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland

Corresponding author: Pradip Dashraath, MRCOG
Department of Obstetrics and Gynaecology,
Division of Maternal–Fetal Medicine,
National University Hospital – SINGAPORE
Phone: (+65) 6772 4285
Email: pradip_dashraath@nuhs.edu.sg

Declaration of interests: We declare no competing interests and have no financial disclosures. Anne Rimoin is director of the affiliated UCLA-DRC Health Research and Training Program in the Democratic Republic of the Congo. This work did not receive any funding.

Keywords: ACAM2000, antiviral, cidofovir, chickenpox, cowpox, COVID-19, monkeypox, miscarriage, MVA-BN, obstetric management, orthopox virus, outbreak, pregnancy, rash, sexual transmission, smallpox, tecovirimat, vaccine, vaccinia immune globulin, vaccinia virus, varicella-zoster, vertical transmission, zoonosis

Short title: Monkeypox and pregnancy

Condensation: Clinicopathological correlations and obstetric management of pregnant women with monkeypox virus infection

Word count (abstract): 326

Word count (main text): 3816

Figures: 4

Tables: 4

Boxes: 2

Supplementary appendix: 3 figures, 1 table

Glossary of terms

- Centrifugal: concentrated on the face and extremities rather than over the trunk
- Clade: group of organisms believed to comprise all the evolutionary descendants of a common ancestor
- MPXV: monkeypox virus – the pathogen that causes human monkeypox infection, first identified in the Democratic Republic of the Congo in 1970 and, prior to 2022, was largely confined to Central and Western Africa
- MPXV clade 1: previously designated 'Congo Basin' clade
- MPXV clades 2 and 3: previously designated 'West African' clade
- Negative pressure room: room that maintains lower air pressure inside the treatment area than that of the surrounding environment, thus preventing internal air from circulating back out
- PHEIC: public health emergency of international concern is defined as an extraordinary event which is determined to constitute a public health risk to other states through the international spread of disease and to potentially require a coordinated international response
- R0: average number of people that a single infected person can be expected to transmit a disease to in a population where all individuals are susceptible to that infection
- TORCH: Toxoplasmosis, Others (including parvovirus B19, syphilis, varicella-zoster virus [VZV], HIV, Hepatitis B and C, Chikungunya, and Zika virus [ZIKV]), Rubella, Cytomegalovirus (CMV), and Herpes simplex virus (HSV)
- WHO: World Health Organisation
- Zoonosis: an infectious disease that has jumped from an animal to humans; zoonotic pathogens may be bacterial, viral or parasitic and can be transmitted to humans through direct contact or through food, water or the environment

ABSTRACT

The 2022 monkeypox outbreak, caused by the zoonotic monkeypox virus, has spread across six WHO regions (the Americas, Africa, Europe, Eastern Mediterranean, Western Pacific and South-East Asia) and was declared a public health emergency of international concern on July 23, 2022. The global situation is especially concerning, given the atypically high rate of person-to-person transmission, suggesting viral evolution to an established human pathogen. Pregnant women are at heightened risk of vertical transmission of the monkeypox virus due to immune vulnerability, natural depletion of population immunity to smallpox among reproductive-age women, and because orthopoxviral cell entry mechanisms can overcome the typically viral-resistant syncytiotrophoblast barrier within the placenta. Pregnancy outcomes following monkeypox infection are scarce but include reports of miscarriage, intrauterine demise, preterm birth and congenital infection. This article aims to forecast the issues maternity units might face and propose management guidelines to protect the health of pregnant women and their fetuses. We review the pathophysiology and clinical features of monkeypox infection and discuss the implications of the unusually high prevalence of anogenital lesions. We describe the use of real-time polymerase chain reaction tests from mucocutaneous and oropharyngeal sites to confirm infection and share an algorithm for the antenatal management of pregnant women with monkeypox virus exposure. Based on the best available knowledge from prenatal orthopoxvirus infections, we discuss the sonographic features of congenital monkeypox and the role of invasive testing in establishing fetal infection. We suggest a protocol for cesarean delivery to avoid the horizontal transmission of the monkeypox virus at birth and address the controversy of mother-infant separation in the postpartum period. Obstetric concerns relating to antiviral therapy with tecovirimat and vaccinia immune globulin, including the risks of QTc prolongation, erroneous blood glucose monitoring and venous thromboembolism, are highlighted. Finally, we discuss the possibility of monkeypox vaccine hesitancy during pregnancy, offer strategies to mitigate these risks and propose research priorities to address knowledge gaps about the impact of monkeypox infection on maternal, fetal, and neonatal health.

Introduction

The global outbreak of human monkeypox – caused by the double-stranded DNA monkeypox virus (MPXV) – was declared a public health emergency of international concern by WHO on July 23, 2022. As of August 1, 2022, the outbreak has resulted in 23,276 laboratory-confirmed infections from 73 non-endemic countries.[1] Epidemiologic observations from the ongoing outbreak suggest a high rate of person-to-person transmission of MPXV clade 3 (the formerly designated 'West African' clade)[2,3] through close physical contact, including during oral, anal and vaginal intercourse.[4]

Although the outbreak has disproportionately affected gay and bisexual men, monkeypox virus infection is neither confined by gender nor sexual orientation and will likely be reported in pregnancies with time and heightened disease surveillance. We believe pregnant women and their fetuses are especially vulnerable for three reasons.

First, the attenuation in cell-mediated immunity by T-helper 1 (Th1) cells due to the physiological shift to a Th2 dominant environment in pregnancy increases maternal susceptibility to viral infections.[5] Th1 cytokines, including type 1 interferon (IFN), inhibit viral replication through direct antiviral and indirect immunoregulatory activities by binding to widely expressed heterodimeric receptors on cell surfaces.[6] MPXV, however, expresses soluble IFNα/β-binding proteins (IFNα/βBP), which interfere with IFN signaling pathways and broadly inhibit antiviral responses in the host.[6] We, therefore, hypothesize that the combination of a gestational bias towards Th2 dominance and IFN evasion by MPXV-induced binding proteins could mediate both susceptibility and enhanced virulence from monkeypox infection in pregnancy.

Second, the eradication of smallpox (a closely related *Orthopoxvirus*) and cessation of the global smallpox vaccination program in 1980 created a niche for monkeypox due to waning population immunity: MPXV infections in Africa have increased at least 10-fold since 1970.[7] The median age at diagnosis has also increased since vaccinations ended, from young children (4 years) in 1970 to young adults (21 years) in 2010-2019.[7] This is reflected in the current 2022 outbreak, where men with a median age of 36 (interquartile range 31 – 43 years) comprise the group with the highest number of infections.[8] Taken together, women presently of reproductive age – defined as 15 to 49 years by WHO[9] – and who are thus, unimmunized are at significant risk of acquiring monkeypox since they lack cross-protective immunity.

Third, vertical transmission and pregnancy loss have been described following MPXV infection.[10,11] Cross-border transmission of monkeypox within populations with no prior immunity and among immunocompromised individuals (at least 41% of cases in the current outbreak are HIV positive[8]) may allow MPXV to acquire mutations which increase virulence and the chance of sustained spread. Monkeypox could thus evolve from a regionally limited zoonosis to a globally endemic infectious disease.[8,12] Pregnancies, particularly in low- and middle-income countries, could then be at

risk – aggravated by the reality that 89% of the estimated 213 million pregnancies yearly occur in resourced-limited settings with the highest probability of poor obstetric and perinatal outcomes.[13]

This article describes the virology and clinical characteristics of monkeypox infection and discusses the disease's vertical transmission potential and management in pregnant women. Where gaps exist, we compare the similarities between monkeypox and other infections and draw on lessons learned from past epidemics. We believe this analysis is essential for developing the principles of obstetric care for pregnant women at risk of monkeypox virus exposure.

Pathogen

MPXV is a brick-shaped, enveloped, 200-250 nm sized, double-stranded DNA, zoonotic virus (Figure 1) of the *Orthopoxvirus* genus in the *Poxviridae* family, which includes smallpox (variola), cowpox, and vaccinia viruses.[14]

The three viral clades of monkeypox – MPXV clade 1 (corresponding to the prior 'Congo Basin' clade)[3] and MPXV clade 2 and 3 (both corresponding to the prior 'West African' clade) – are clinically relevant. Clade 1 is associated with severe disease and a case fatality rate (CFR) approximately three times that of clades 2 and 3 (clade 1 CFR 10,6% [95% CI 8,4–13,3] *vs* clade 2/3 CFR 3,6% [95% CI 1,7–6,8]).[7,15]

Person-to-person transmission of MPXV classically occurs through large respiratory droplets, close contact with skin lesion exudates, and contaminated fomites. Pooled estimates suggest a secondary attack rate of approximately 8% (range 0–11%) among household contacts who are unvaccinated against smallpox.[16] Sexual transmission might be possible given the detection of MPXV DNA in seminal fluid and the high rate of primary genital and anal mucosal lesions following condomless sexual activity in the 2022 outbreak.[17] The caveat, however, is that isolating MPXV in seminal fluid is not necessarily evidence of infectivity because viremia is known to seed the reproductive tract.[18] The basic reproduction number, R0, for monkeypox is estimated to be 0.8 but >1 among men who have sex with men.[19] For context, SARS-CoV-2 has a strain-dependent R0 of 2.5 (original strain), 7 (delta variant B.1.617.2) and 10 (omicron variant), respectively[20], while smallpox had an R0 between 3.5 – 6.[21]

Because of their large DNA (~197 kb), orthopoxviruses are better at detecting and repairing mutations than RNA viruses (e.g., SARS-CoV-2). Consequently, this had resulted in only 1-2 substitutions per genome per year, which made MPXV a virus with presumably low epidemic potential.[22,23] However, genomic sequencing studies have revealed that the 2022 MPXV strain contains 6-12 times the expected number of single-nucleotide polymorphisms, suggesting accelerated evolution and increased human adaptation.[2] These might have contributed to cryptic human transmission of monkeypox for years before the global outbreak was amplified by super-spreading events in 2022.

Pathophysiology

The phases of MPXV viremia help correlate the signs and symptoms of monkeypox infection.[24,25] Following exposure to MPXV from any route (e.g., oropharynx, nasopharynx, intradermal and possibly anogenital [as seen in the 2022 outbreak]), the virus replicates at the site of inoculation before spreading to locoregional lymph nodes. From there, MPXV enters the bloodstream, producing a primary viremia that seeds the hematopoietic system. The duration of primary viremia corresponds with the incubation period of monkeypox infection (7 – 14 days with an upper limit of 21 days). Further replication of MPXV produces a secondary viremia, which results in a prodrome lasting approximately two days, characterized by fever, headache, myalgia, and tender lymphadenopathy. The latter may be cervical or inguinal (1 – 4 cm in diameter) and is typical of monkeypox infection. Approximately 1 – 3 days following the onset of fever, MPXV seeds the skin and mucous membranes with virions at various stages of assembly within the cytoplasm of keratinocytes. This causes an enanthem (oral cavity lesions) and a skin exanthem due to ballooning degeneration of basal keratinocytes and full thickness necrosis of the epidermis.[26]

Clinical features of monkeypox in non-pregnant individuals

The rash, typically centrifugal over the face and extremities, progresses from macules, papules, vesicles, pustules, and finally to crusts (Figure 2) and is the most common symptom seen in over 90% of patients in the present outbreak.[8] Patients are infectious from the onset of fever until the vesicles have scabbed. Extracutaneous manifestations include pneumonia, ocular complications, encephalitis and secondary soft-tissue infections.

Atypical features of the ongoing outbreak, however, are a high rate of genital, perianal and oral lesions and rash that does not evolve synchronously, including erythematous maculopapular rash of rapid onset separate from areas of vesicles or pustules (supplementary appendix).[27] Among 528 laboratory-confirmed monkeypox virus infections between April – June 2022, 73% had anogenital lesions and 10% presented with only a solitary genital ulcer, which could be easily misdiagnosed as a sexually-transmitted infection and exacerbate community transmission of monkeypox until the correct diagnosis is established.[17] It is unclear if monkeypox virus within the anorectum and external genitalia is the consequence of mucosal seeding during viremia or the virus propagating at the site of initial exposure. Additionally, lymphadenopathy, while characteristic of monkeypox, was only present in one-third of all cases reported to WHO as of July 22, 2022.[8]

Clinical features of monkeypox in pregnancy

Information about clinical characteristics, vertical transmission potential, maternal complications, and fetal outcomes of monkeypox infection in pregnancy are limited.

Among four pregnant women from the Democratic Republic of Congo (DRC) with laboratory-confirmed MPXV between March 2007 to July 2011, one woman with mild disease delivered a neonate at term with no clinical features of monkeypox infection.[10] However, three women with moderate-to-severe maternal infection had adverse obstetric outcomes: two had spontaneous first-trimester miscarriages at 6 weeks' gestation (with a maternal MPXV viral load of 3.5×10^3 and 7.9×10^5 gene copies/ml respectively) and one had a second-trimester loss at 18 weeks' gestation (viral load of 8.9×10^5 gene copies/ml). The stillborn fetus had a vesicular rash, hepatomegaly, and hydrops with a high viral load ($>10^7$ genome copies/mL) detected in fetal tissue, umbilical cord, and placenta – confirming vertical transmission of MPXV. Another woman with maternal infection at 24 weeks' gestation had a preterm delivery at 30 weeks' gestation; that neonate had a generalized rash at birth resembling monkeypox.[11] Although not reported, we make the assumption that all five of these women were probably infected with MPXV clade 1 given they were from the DRC. However, the risk factors associated with adverse pregnancy outcomes in monkeypox infection are presently unknown.

How did smallpox compare?

Monkeypox and smallpox (caused by the variola virus) are orthopoxviruses with striking similarities: the clinical features of both infections include an incubation period of about 14 days, a two-day prodrome with fever, and a centrifugal vesiculopustular rash.[28] At the molecular level, the central genomic region of MPXV is 96,3% identical to the variola virus, and the amino acid sequences of the virion proteins encoded in this region are up to 99,2% homologous.[29] Additionally, like MPXV, there are two distinct strains of smallpox with varying mortality risks: variola major with a CFR of 30–50% and variola minor with a CFR of less than 2%.[30]

The overall maternal CFR from smallpox infection in pregnancy was 34,3% (95%CI 31,4–37,1), and the crude proportion of miscarriage and preterm birth was 39,9% (95%CI 36,5–43,2).[31] Smallpox likely represents the extreme end of the spectrum of orthopox infection outcomes during pregnancy. In the largest series of 389 pregnant women with smallpox, 75% miscarried before 24 weeks' gestation, 55% delivered preterm, and 10% suffered stillbirths at term.[32] Congenital smallpox occurred in 9% of fetuses and resulted in a neonatal mortality rate of 100%. Maternal mortality from smallpox was the highest in the third trimester of pregnancy; expectant mothers were 2 – 4 times more likely than non-pregnant women to die from the infection and vaccinated pregnant women were about three times less likely to succumb than those who were unvaccinated.[32] Hemorrhagic smallpox – characterized by petechiae, ecchymoses, profound thrombocytopenia and multi-organ failure – occurred seven times more frequently during pregnancy than in men and non-pregnant women regardless of vaccination status and carried a CFR of 100%.[33]

However, monkeypox and smallpox differ in the regions encoding virulence factors (e.g., IFN resistance genes and interleukin-1β inhibitors) at the terminal ends of the viral genome which might explain the variation in clinical presentation and disease severity between the two infections.[6] Additionally, no hemorrhagic form of monkeypox has been described in humans, although MPXV clade 1 has demonstrated the potential for pulmonary hemorrhage, epistaxis, and impaired coagulation parameters in animal studies.[34]

What about monkeypox and varicella-zoster co-infection?

The possibility of monkeypox and varicella-zoster virus (VZV) co-infection, seen in 10% – 13% of individuals in the DRC[35,36], is an epidemiologic observation worth highlighting because women from tropical and subtropical regions are more likely to be non-immune to VZV. For example, only 80,9% of pregnant women in Tunisia[37] have VZV IgG antibodies compared to 96,1% and 98,8% of pregnant women in Spain and France.[38,39] Co-infection carries important implications for similarly susceptible groups because both viruses carry a risk of vertical transmission. Given that co-infection also modifies the severity of the skin rash, delayed diagnoses and treatment could result in worse perinatal outcomes, particularly in resource-limited settings.[4,35,36]

Possible mechanisms and risk of *in-utero* transmission of monkeypox

There is currently no data demonstrating the mechanisms employed by the monkeypox virus to traverse the maternal-placental-fetal barrier and infect fetal tissues. Multiple mechanisms are possibly involved in the ability of MPXV to invade placental trophoblast cells, particularly because the virus does not express cell-specific receptors facilitating cell tropism – unlike most other viruses which have evolved distinct cell-specific strategies for cell entry and replication within host cells.[40] MPXV may reach the fetus via the haematogenous route, arriving at the intervillous space from maternal uterine spiral arteries, binding to trophoblast cells and consecutively infecting syncytiotrophoblasts, cytotrophoblasts, fetal endothelial cells within the floating or anchored villi, and eventually fetal blood cells. MPXV may also ascend directly from genital lesions via cervical and uterine tissue, directly colonizing the chorionic membranes and decidua.[41] In murine models of vaccinia virus infection during pregnancy via intravenous and intraperitoneal routes, harvested placenta initially amplified vaccinia-specific viral mRNA only in cells adjacent to maternal blood vessels but not on the fetal side, and only amplified viral mRNA on in fetal vessels a few days later, demonstrating the time required for contiguous spread from mother to fetus.[42] Cytopathic effects in human syncytiotrophoblasts observed in placenta infected with vaccinia virus include cytoplasmic condensation and cell rounding.[43,44]

Fetal and placental damage following vertical transmission can be additionally inferred from a report of early pregnancy fetal loss in a woman infected with cowpox virus (CPXV), an orthopoxvirus

sharing a close genetic relationship to MPXV and is similarly capable of causing zoonotic infections in humans.[45] Pregnancy loss in a dairy worker with cowpox occurred at 11 weeks' gestation as a consequence of viraemia;[46] DNA extracted from maternal blood, pustular areas, and from fetal and placental tissues confirmed CPXV infection by amplification of the A27L (for orthopoxvirus) and D8L/D11L genes (specific for CPXV), and viral cytopathic effects were observed on electron microscopy.[47] In vertical transmission of smallpox, stillborn fetuses showed dermal pox signs and viral particles were isolated from fetal skin and other organs. Placental pathology demonstrated necrotic villi, fibrin deposition, cytopathic effects (inflammatory infiltrates, necrosis) and virions at various stages of assembly on electron microscopy.[26,41]

Taken together, we speculate that MPXV might breach the maternal-placental-fetal barrier via viral fusion with trophoblasts, a process by which viral capsid proteins adhere to target cell surface receptors initiating configurational changes in the viral capsid, enabling internalization of viral DNA through fusion with syncytiotrophoblast membrane or via transcytosis.[48] Internalized viruses can then replicate and cause host cell damage directly (cytopathic effects) or secondarily to local inflammatory and immune reactions from the host. Once the placental barrier is breached, MPXV might be able to infect multiple placental cells, enabling it to reach the fetal bloodstream eventually. Fetal hydrops and hepatomegaly observed in MPXV-infected fetuses may reflect the extent of placental damage and resultant hypoxia from similar effects. It is also unknown whether maternal viral infection with MPXV (particularly in the third trimester) and maternal immune activation during pregnancy – as seen in HIV[49] and more recently with SARS-CoV-2[50] - might affect childhood neurodevelopmental milestones in fetuses exposed to monkeypox in-utero.

Approach to the management of monkeypox in pregnancy

Diagnosis

Taking all the above features of monkeypox into consideration, monkeypox infection should be suspected in any pregnant woman who presents with:

1) Unexplained skin rash or genital ulcer (see Box 1 for differential diagnoses) OR
2) One or more symptoms of fever, headache, myalgia, asthenia or lymphadenopathy AND
3) Within the last 21 days:
    a. Had a travel history to countries with recently reported cases of monkeypox; OR
    b. Had a history of close contact with an infected person; OR
    c. Had a history of casual sexual contact during travel

Box 1

Appearance of monkeypox lesion	Differential diagnoses in pregnancy
Maculopapular rash	• Measles • Rubella • Cytomegalovirus and toxoplasmosis • Secondary syphilis • Atopic eruption of pregnancy • Pruritic urticarial papules and plaques of pregnancy
Vesiculopustular rash	• Varicella zoster • Pemphigoid gestationis • Hand-foot-and-mouth disease
Anogenital ulcer	• Herpes simplex • Lymphogranuloma venereum

Because of the atypical features of monkeypox infection in the current outbreak, clinicians must maintain a high index of suspicion and conduct a thorough physical examination, with PPE (Table 1), including an assessment of oral, vaginal and perianal regions. Given that the monkeypox rash can co-exist with sexually transmitted infections[17] or be confused with other dermatoses, we suggest broadly excluding common causes of vesiculopustular rash in pregnancy with polymerase chain reaction (PCR) tests, including that of herpes simplex, varicella zoster and syphilis.

Real-time PCR from swabs of vesicle fluid or scabs from at least two sites placed in viral transport media is the gold standard for the diagnosis of monkeypox[51], because viral DNA will be present within cutaneous lesions due to seeding from secondary viremia. False-negative results might occur due to poor specimen quality, improper handling, or DNA extraction failure. Patients reporting high-risk exposure and experiencing a febrile prodrome before the onset of skin rash can undergo a PCR throat swab. Monkeypox viral load in the upper respiratory tract peaks early in the infection, and so oropharyngeal sampling in this context demonstrates high detection rates, second only to cutaneous lesions.[52,53] In contrast, PCR of EDTA blood samples may aid, but not replace, mucocutaneous sampling because the duration of monkeypox viremia is short (i.e., corresponding with the prodrome, which lasts approximately two days), and plasma may thereafter not contain high levels of MPXV. In the current outbreak, a positive PCR result was most commonly obtained from skin or anogenital lesions.[17]

Antenatal care and fetal surveillance

Given the possible vertical transmission of monkeypox virus, serial ultrasound surveillance for signs of congenital infection is justified in symptomatic pregnant women with PCR-confirmed disease.

Additionally, we are of the opinion that pauci-symptomatic and asymptomatic pregnant women with high-risk monkeypox exposure who test positive on oropharyngeal RT-PCR should also undergo ultrasound screening, given the currently unquantifiable risk to the fetus. By extrapolating the known obstetric outcomes of monkeypox infection, the sonographic features of fetal infection might include hepatomegaly, ascites, hydrops, placental calcifications and fetal growth restriction (Figure 3).[54]

In the presence of these features, amniocentesis with real-time PCR could establish the diagnosis of fetal infection. However, the sensitivity of molecular detection of MPXV in amniotic fluid is presently unknown. By analogy with other TORCH infections, MPXV is likely shed in the amniotic fluid once sufficient time has elapsed for the virus to breach the placental barrier (typically 6–8 weeks after infection), once the fetal kidneys produce sufficient urine (i.e., after 16-18 weeks' gestation), or fetal skin lesions have developed.[55] It is theoretically possible that MPXV might only be transiently detected *in-utero* (similar to Zika virus in amniotic fluid, placenta or fetal tissues[56]), despite a progressive risk of fetal anomalies throughout pregnancy – the kinetics of MPXV within the fetal compartment is an area that warrants further study.

Labor and delivery

Monkeypox infection in the third trimester or during the last four weeks of pregnancy should not indicate expediting delivery unless directed by obstetric factors or clinical urgency in critically ill women. Characterization of acute-phase humoral immunity to monkeypox suggests seroconversion for both IgG and IgM approximately four days after the onset of rash in unvaccinated individuals.[57] Thus, by additional analogy with varicella-zoster, deferring delivery for at least seven days after the onset of monkeypox rash might permit the transplacental transfer of maternal IgG antibodies against MPXV.

Cesarean section with PPE would be the most reasonable delivery strategy in women with monkeypox infection (Table 2). Like neonatal varicella[58] (50% risk of transmission, 20% CFR) and neonatal herpes simplex[59] (85% risk of transmission, 60% CFR), exposure to anogenital MPXV during vaginal delivery may carry a high risk of fulminant neonatal sepsis, including encephalitis, sight-threatening keratitis, and necrotizing skin infections.[28]

Maternal anesthetic concerns include complications from neuraxial anesthesia (given the risk of transmitting cutaneous MPXV from the trunk into the central nervous system) and intubation (if oropharyngeal lesions are present). In women with widespread rash, extended-spectrum antibiotic cover with cefazolin plus azithromycin before skin incision is likely to reduce the risk of post-cesarean endometritis and surgical site infection (SSI) to a greater extent than cefazolin alone. Anaphylaxis is an under-recognized but potentially fatal complication following topical chlorhexidine exposure to broken skin and mucosa.[60] Therefore, in women with significant mucocutaneous involvement in monkeypox, we opine that povidone-iodine for antiseptic skin and vaginal preparation is probably safer even though chlorhexidine-alcohol is more effective in lowering SSI risk after cesarean delivery.[61]

Management of the newborn depends on the likelihood of vertical transmission, and intravenous vaccinia immune globulin (VIGIV) could be considered in neonates with a high risk of perinatally acquired monkeypox (Table 3). Although it is unknown if MPXV is present in breastmilk, the infection might be transmitted to the newborn through close contact during breastfeeding. It would therefore be prudent to delay breastfeeding until the mother's rashes have scabbed over. If, however, the patient chooses to breastfeed, the nipple-areolar complex should be free of lesions, the neonate should be fully swaddled to reduce skin-to-skin contact, and the patient should wear a face mask to reduce droplet transmission, owing to the close proximity between mother and child. Given the currently unquantifiable and unknown risks to the neonate, we also propose that pediatricians consider neurocognitive phenotyping of the infant to detect developmental disorders of motor function, speech, language, and other deficits relating to possible maternal immune activation by MPXV in-utero.

Antiviral treatment and vaccines

Tecovirimat, which inhibits the orthopoxvirus VP37 envelope wrapping protein, is the first-line antiviral recommended by the US CDC for the treatment of monkeypox in critically ill pregnant and breastfeeding women.[62] Although tecovirimat is not authorized for use during pregnancy, animal studies have shown no embryotoxic and teratogenic effects. VIGIV is also likely to be safe, given that immunoglobulins, as a class, have been used widely in pregnancy without adverse outcomes. Since tecovirimat and VIGIV will feature prominently in the pharmacological management of monkeypox, clinicians must be aware of the unique obstetric issues when using these agents (Table 4).

For pre- and post-exposure prophylaxis in pregnancy, WHO recommends the non-replicating smallpox vaccine (MVA-BN), which confers 85% cross-protective immunity against monkeypox infection.[63] To date, 300 pregnant women have received the MVA-BN vaccine without incident.[64] In contrast, ACAM2000 is a live, replicating smallpox vaccine that is more heavily stockpiled but carries a risk of fetal vaccinia, which can result in preterm delivery, stillbirth, neonatal death and adverse maternal reactions.[65] Pregnant healthcare workers and others with significant exposure (e.g., pregnant household contacts) must, therefore, be prioritized for the MVA-BN vaccine when indicated.

However, as with influenza, pertussis and Covid-19 vaccination[66–68], we anticipate barriers to acceptance, and so we propose strategies aimed at the pregnant woman, healthcare provider and institutional review board (IRB) to improve the uptake of monkeypox vaccination during pregnancy (Figure 4). The Monitored Emergency Use of Unregistered and Experimental Interventions (MEURI) framework from the WHO[69] and the PREVENT working group[70] roadmap should be used by healthcare systems to guide the ethical use of expanded-access drugs and facilitate the deployment of vaccines in pregnancy.

Conclusions and recommendations

For years, the scientific community has warned that monkeypox could emerge as the most crucial orthopoxvirus infection in humans.[7,12] The disease will be a challenge for pregnant individuals, who represent a vulnerable population during any public health emergency of international concern. For now, much of the obstetric management will be based on consensus and best practice recommendations. We propose the following research priorities for clinicians and health systems (Box 2) to supplement WHO's recommendations to guide the global effort to tackle monkeypox – now and in the future.[71]

REFERENCES

1. CDC. 2022 monkeypox and orthopox virus outbreak global map. Accessed July 27, 2022. https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html

2. Isidro J, Borges V, Pinto M, et al. Phylogenomic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus. *Nat Med*. Published online June 24, 2022. doi:10.1038/s41591-022-01907-y

3. Christian Happi1,2*, Ifedayo Adetifa3, Placide Mbala4, Richard Njouom5, Emmanuel Nakoune6, Anise Happi1, Nnaemeka Ndodo3, Oyeronke Ayansola3, Gerald Mboowa7, Trevor Bedford8,9, Richard A. Neher10,11, Cornelius Roemer10,11, Emma Hodcroft11,12,13, Houriiyah Tegally14,15, Áine O'Toole16, Andrew Rambaut16, Oliver Pybus17,18,19, Moritz U.G. Kraemer17,18, Eduan Wilkinson14, Joana Isidro20, Vítor Borges20, Miguel Pinto20, João Paulo Gomes20, Cheryl Baxter15,21, Richard Lessells14,21, Ahmed E. Ogwell7, Yenew Kebede7, Sofonias K. Tessema7, Tulio de Oliveira14,15,21,22*. Urgent need for a non-discriminatory and non-stigmatizing nomenclature for monkeypox virus. https://virological.org/t/urgent-need-for-a-non-discriminatory-and-non-stigmatizing-nomenclature-for-monkeypox-virus/853

4. WHO. Clinical management and infection prevention and control for monkeypox. Interim rapid response guidance. Published online June 10, 2022. Accessed June 11, 2022. https://www.who.int/publications/i/item/WHO-MPX-Clinical-and-IPC-2022.1

5. Randall RE, Goodbourn S. Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. *J Gen Virol*. 2008;89:1-47.

6. Marco MM F, A A, P H, IK D, A A. The highly virulent variola and monkeypox viruses express secreted inhibitors of type I interferon. *FASEB J*. 2010;24:1479-1488.

7. Bunge EM, Hoet B, Chen L. The changing epidemiology of monkeypox – a potential threat? A systematic review. *PLoS Negl Trop Dis*. 2022;16:e0010141.

8. WHO Multi-country outbreak of monkeypox, External situation report #2 - 25 July 2022. Accessed July 27, 2022. https://www.who.int/publications/m/item/multi-country-outbreak-of-monkeypox--external-situation-report--2---25-july-2022

9. WHO. MATERNAL, NEWBORN, CHILD AND ADOLESCENT HEALTH AND AGEING. https://www.who.int/data/maternal-newborn-child-adolescent-ageing/indicator-explorer-new/mca/women-of-reproductive-age-(15-49-years)-population-(thousands)

10. Mbala PK, Huggins JW, T RR. Maternal and fetal outcomes among pregnant women with human monkeypox infection in the Democratic Republic of Congo. *J Infect Dis*. 2017;216:824-828.

11. Kisalu NK, Mokili JL. Toward understanding the outcomes of monkeypox infection in human pregnancy. *J Infect Dis*. 2017;216:795-797.

12. Sklenovska N, Ranst M. Emergence of monkeypox as the most important orthopoxvirus infection in humans. *Front Public Health*. 2018;6(241).

13. Bardaji A, Sevene E, Cutland C. The need for a global COVID-19 maternal immunisation research plan. *Lancet*. 2021;397:e17-18.

14. Parker S, Nuara A, Buller RML, Schultz DA. Human monkeypox: an emerging zoonotic disease. *Future Microbiol*. 2007;2(1):17-34. doi:10.2217/17460913.2.1.17

15. Otu A, Ebenso B, Walley J, Barceló JM, Ochu CL. Global human monkeypox outbreak: atypical presentation demanding urgent public health action. *Lancet Microbe*. Published online June 7, 2022:S2666-5247(22)00153-7. doi:10.1016/S2666-5247(22)00153-7

16. Beer EM, Rao VB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. *PLoS Negl Trop Dis*. 2019;13(10):e0007791. doi:10.1371/journal.pntd.0007791

17. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox Virus Infection in Humans across 16 Countries - April-June 2022. *N Engl J Med*. Published online July 21, 2022. doi:10.1056/NEJMoa2207323

18. A LT, G M, D M. From ancient to emerging infections: the odyssey of viruses in the male genital tract. *Physiol Rev*. 2020;100:1349-1414.

19. Second meeting of the International Health Regulations (2005) (IHR) Emergency Committee regarding the multi-country outbreak of monkeypox. https://www.who.int/news/item/23-07-2022-second-meeting-of-the-international-health-regulations-(2005)-(ihr)-emergency-committee-regarding-the-multi-country-outbreak-of-monkeypox

20. Burki TK. Omicron variant and booster COVID-19 vaccines. *Lancet Respir Med*. 2022;10(2):e17. doi:10.1016/S2213-2600(21)00559-2

21. Gani R, Leach S. Transmission potential of smallpox in contemporary populations. *Nature*. 2001;414(6865):748-751. doi:10.1038/414748a

22. Firth C, Kitchen A, Shapiro B, Suchard MA, Holmes EC, Rambaut A. Using time-structured data to estimate evolutionary rates of double-stranded DNA viruses. *Mol Biol Evol*. 2010;27(9):2038-2051. doi:10.1093/molbev/msq088

23. Reynolds MG, Carroll DS, Karem KL. Factors affecting the likelihood of monkeypox's emergence and spread in the post-smallpox era. *Curr Opin Virol*. 2012;2(3):335-343. doi:10.1016/j.coviro.2012.02.004

24. Goff AJ, Chapman J, Foster C, et al. A novel respiratory model of infection with monkeypox virus in cynomolgus macaques. *J Virol*. 2011;85(10):4898-4909. doi:10.1128/JVI.02525-10

25. Mucker EM, Wollen-Roberts SE, Kimmel A, Shamblin J, Sampey D, Hooper JW. Intranasal monkeypox marmoset model: Prophylactic antibody treatment provides benefit against severe

monkeypox virus disease. *PLoS Negl Trop Dis*. 2018;12(6):e0006581. doi:10.1371/journal.pntd.0006581

26. Bayer-Garner IB. Monkeypox virus: histologic, immunohistochemical and electron-microscopic findings. *J Cutan Pathol*. 2005;32(1):28-34. doi:10.1111/j.0303-6987.2005.00254.x

27. Patel A, Bilinska J, Tam JCH, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ*. 2022;378:e072410. doi:10.1136/bmj-2022-072410

28. McCollum AM, Damon IK. Human monkeypox. *Clin Infect Dis*. 2014;58:260-267.

29. Shchelkunov SN, Totmenin AV, Babkin I. Human monkeypox and smallpox viruses: genomic comparison. *FEBS Letters 2001;509;66-70*.

30. Shchelkunov SN, Totmenin AV, Vladimir N. Alastrim smallpox variola minor virus genome DNA sequences. *Virology*. 2000;266:361-386.

31. Nishiura H. Smallpox during pregnancy and maternal outcomes. *Emerg Infect Dis*. 2006;12:1119-1121.

32. Rao AR, Prahlad I, Swaminathan M, Lakshmi A. Pregnancy and smallpox. *J Indian Med Assoc*. 1963;40:353-363.

33. Suarez VR, Hankins GDV. Smallpox and pregnancy: from eradicated disease to bioterrorist threat. *Obstet Gynecol*. 2002;100:87-93.

34. Sbrana E, Xiao SY, Newman PC, Tesh RB. Comparative pathology of North American and Central African strains of monkeypox virus in a ground squirrel model of the disease. *Am J Trop Med Hyg*. 2007;76:155-164.

35. Hughes CM, Liu L, WB D. A tale of two viruses: coinfections of monkeypox and varicella zoster virus in the Democratic Republic of Congo. *Am J Trop Med Hyg*. 2021;104:604-611.

36. Hoff NA, Morier DS, NK K. Varicella coinfection in patients with active monkeypox in the Democratic Republic of the Congo. *EcoHealth*. 2017;14:564-574.

37. Hussey H, Abdullahi L, J C. Varicella zoster virus-associated morbidity and mortality in Africa – a systematic review. *BMC Infect Dis*. 2017;17(717).

38. Plans P, Costa J, Espuñes J, Plasència A, Salleras L. Prevalence of varicella-zoster antibodies in pregnant women in Catalonia (Spain). Rationale for varicella vaccination of women of childbearing age. *BJOG*. 2007;114:1122-1127.

39. Saadatian-Elahi M, Mekki Y, Del Signore C, Lina B, Derrough T, Caulin E. Seroprevalence of varicella antibodies among pregnant women in Lyon-France. *Eur J Epidemiol*. 2007;22:405-409.

40. Zaga-Clavellina V, Diaz L, Olmos-Ortiz A, Godínez-Rubí M, Rojas-Mayorquín AE, Ortuño-Sahagún D. Central role of the placenta during viral infection: Immuno-competences and miRNA defensive responses. *Biochim Biophys Acta Mol Basis Dis*. 2021;1867(10):166182. doi:10.1016/j.bbadis.2021.166182

41. Fuentes-Zacarías P, Murrieta-Coxca JM, Gutiérrez-Samudio RN, et al. Pregnancy and pandemics: Interaction of viral surface proteins and placenta cells. *Biochim Biophys Acta Mol Basis Dis*. 2021;1867(11):166218. doi:10.1016/j.bbadis.2021.166218

42. Benning N, Hassett DE. Vaccinia virus infection during murine pregnancy: a new pathogenesis model for vaccinia fetalis. *J Virol*. 2004;78(6):3133-3139. doi:10.1128/jvi.78.6.3133-3139.2004

43. Nørskov-Lauritsen N, Zachar V, Petersen PM, Hager H, Aboagye-Mathiesen G, Ebbesen P. In vitro infection of human placental trophoblast by wild-type vaccinia virus and recombinant virus expressing HIV envelope glycoprotein. *Res Virol*. 1992;143(5):321-328. doi:10.1016/s0923-2516(06)80120-2

44. Schmidt FI, Bleck CKE, Helenius A, Mercer J. Vaccinia extracellular virions enter cells by macropinocytosis and acid-activated membrane rupture. *EMBO J*. 2011;30(17):3647-3661. doi:10.1038/emboj.2011.245

45. Bourquain D, Dabrowski PW, Nitsche A. Comparison of host cell gene expression in cowpox, monkeypox or vaccinia virus-infected cells reveals virus-specific regulation of immune response genes. *Virol J*. 2013;10:61. doi:10.1186/1743-422X-10-61

46. Ferrier A, Frenois-Veyrat G, Schvoerer E, et al. Fatal Cowpox Virus Infection in Human Fetus, France, 2017. *Emerg Infect Dis*. 2021;27(10):2570-2577. doi:10.3201/eid2710.204818

47. Maksyutov RA, Gavrilova EV, Meyer H, Shchelkunov SN. Real-time PCR assay for specific detection of cowpox virus. *J Virol Methods*. 2015;211:8-11. doi:10.1016/j.jviromet.2014.10.004

48. León-Juárez M, Martínez-Castillo M, González-García LD, et al. Cellular and molecular mechanisms of viral infection in the human placenta. *Pathog Dis*. 2017;75(7). doi:10.1093/femspd/ftx093

49. Wedderburn CJ, Weldon E, C BC. Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis. *Lancet Child Adolesc Health*. 2022;6:393-408.

50. Edlow AG, Castro VM, LL S. Neurodevelopmental outcomes at 1 year in infants of mothers who tested positive for SARS-CoV-2 during pregnancy. *JAMA Netw Open*. 2022;5:e2215787.

51. WHO. WHO Laboratory testing for the monkeypox virus: interim guidance. Published online May 23, 2022. Accessed August 1, 2022. https://www.who.int/publications/i/item/WHO-MPX-laboratory-2022.1

52. Adler H, Gould S, Hine P, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis*. Published online May 24, 2022:S1473-3099(22)00228-6. doi:10.1016/S1473-3099(22)00228-6

53. Noe S, Zange S, Seilmaier M, et al. Clinical and virological features of first human monkeypox cases in Germany. *Infection*. Published online July 11, 2022. doi:10.1007/s15010-022-01874-z

54. Dashraath P, Nielsen-Saines K, Mattar C, Musso D, Tambyah P, Baud D. Guidelines for pregnant individuals with monkeypox virus exposure. *Lancet*. 2022;400(10345):21-22. doi:10.1016/S0140-6736(22)01063-7

55. Khalil A, Sotiriadis A, R C. ISUOG practice guidelines: role of ultrasound in congenital infection. *Ultrasound Obstet Gynecol*. 2020;56:128-151.

56. Schaub B, Vouga M, F N. Analysis of blood from Zika virus-infected fetuses: a prospective case series. *Lancet Infect Dis*. 2017;17:520-527.

57. Karem KL, Reynolds M, Braden Z, et al. Characterization of Acute-Phase Humoral Immunity to Monkeypox: Use of Immunoglobulin M Enzyme-Linked Immunosorbent Assay for Detection of Monkeypox Infection during the 2003 North American Outbreak. *Clin Diagn Lab Immunol*. 2005;12(7):867-872. doi:10.1128/CDLI.12.7.867-872.2005

58. Sauerbrei A, Wutzler P. Neonatal varicella. *J Perinatol*. 2001;21:545-549.

59. Looker KJ, Magaret AS, MT M. First estimates of the global and regional incidence of neonatal herpes infection. *Lancet Glob Health*. 2017;5:e300-309.

60. Rose MA, Garcez T, Savic S, Garvey LH. Chlorhexidine allergy in the perioperative setting: a narrative review. *British Journal of Anaesthesia*. 2019;123(1):e95-e103. doi:10.1016/j.bja.2019.01.033

61. Tuuli MG, Liu J, Stout MJ, et al. A Randomized Trial Comparing Skin Antiseptic Agents at Cesarean Delivery. *New England Journal of Medicine*. 2016;374(7):647-655. doi:10.1056/NEJMoa1511048

62. Clinical Considerations for Monkeypox in People Who are Pregnant or Breastfeeding. Published online July 18, 2022. Accessed August 1, 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/pregnancy.html

63. W.H.O. Vaccines and immunisation for monkeypox. Interim guidance. *Published 14*. Published online June 2022. https://www.who.int/publications/i/item/who-mpx-immunization-2022.1

64. European Medicines Agency. Summary of product characteristics – Imvanex. https://www.ema.europa.eu/en/documents/product-information/imvanex-epar-product-information_en.pdf.

65. Kozlov M. Monkeypox vaccination begins - can the global outbreaks be contained? *Nature*. 2022;606(7914):444-445. doi:10.1038/d41586-022-01587-1

66. Qiu X, Bailey H, Thorne C. Barriers and Facilitators Associated With Vaccine Acceptance and Uptake Among Pregnant Women in High Income Countries: A Mini-Review. *Front Immunol*. 2021;12:626717. doi:10.3389/fimmu.2021.626717

67. Dashraath P, Nielsen-Saines K, Madhi SA, Baud D. COVID-19 vaccines and neglected pregnancy. *The Lancet*. 2020;396(10252):e22. doi:10.1016/S0140-6736(20)31822-5

68. Stuckelberger S, Favre G, Ceulemans M, et al. SARS-CoV-2 Vaccine Willingness among Pregnant and Breastfeeding Women during the First Pandemic Wave: A Cross-Sectional Study in Switzerland. *Viruses*. 2021;13(7):1199. doi:10.3390/v13071199

69. W.H.O. Emergency use of unproven clinical interventions outside clinical trials: ethical considerations. https://apps.who.int/iris/rest/bitstreams/1416840/retrieve.

70. Krubiner CB, Faden RR, RA K. Pregnant women and vaccines against emerging epidemic threats: ethics guidance for preparedness, research, and response. *Vaccine*. 2021;39:85-120.

71. WHO meeting on monkeypox research priorities. *Meeting summary*. https://cdn.who.int/media/docs/default-source/blue-print/day-2_meeting-summary_monkeypox-meeting_03june2022.pdf?sfvrsn=f4ec1066_3.

Figure 1: Monkeypox virus

Panel A shows the monkeypox virus on transmission electron microscopy, negative staining (bar = 200 nm). Panel B shows a cut-away line drawing of the monkeypox virus. E = envelope; OM = outer membrane; CM = core membrane; LB = lateral body; N = nucleosome; ST = surface tubules. Tecovirimat targets the VP37 protein and inhibits formation of the viral envelope (E). Cidofovir targets DNA polymerase within the viral nucleosome (N) but is teratogenic, unlike tecovirimat.

Image credit: Panel A – Andrea Männel 2001/ RKI Robert Koch Institute; Panel B – Authors' original illustration using Biorender

Figure 2: Monkeypox rash

Characteristic vesicular (Panel A) and pustular (Panel B) lesions in a person with PCR-confirmed human monkeypox infection.

Figure 3: Management of monkeypox during pregnancy

Figure 4: Possible barriers to monkeypox vaccination during pregnancy

IRB = institutional review board; HCP = healthcare provider; ACOG = American College of Obstetricians and Gynecologists; ACNM = American College of Nurse-Midwives; RCOG = Royal College of Obstetricians and Gynecologists; FIGO = International Federation of Gynecology and Obstetrics; LMIC = low- and middle-income countries

Table 1: Infection prevention and control (IPC) recommendations for staff attending to a pregnant patient with suspected monkeypox infection

Examples of clinical encounters in obstetrics	Recommended PPE and other IPC measures
Healthcare staff with direct patient contact e.g., • Patient transport (including paramedic staff) • Obstetric (including vaginal) examination • Ultrasonography (including vaginal scans) • Delivery • Pathology (for placenta/fetal tissue examination)	○ Gloves ○ Surgical cap ○ N95/FFP2 respirator ○ Gowns with long sleeves* ○ Goggles or disposable face shields * *Gowns should be fluid-impermeable or AAMI level 4 equivalent*
Housekeeping staff with high-risk exposure e.g., • Cleaning operating room after delivery • Handling potentially infected waste (including placental tissue and soiled linen)	○ Gloves ○ Surgical cap ○ N95/FFP2 respirator ○ Gowns with long sleeves* ○ Goggles or disposable face shields ○ Boots or shoe covers should be considered *Other IPC measures* ○ All waste and soiled linen should be considered infectious and double-bagged with an inner water-soluble layer ○ Labor and operating rooms occupied by pregnant women with confirmed monkeypox should be terminally cleaned with bleach-based disinfectants (i.e., 1000 ppm) ○ Adjunct use of UV-C disinfection systems or hydrogen peroxide vaporization (HPV) systems would be prudentPatients'ts' own clothing (if not discarded) may be bagged and brought home for laundering in a standard washing machine using 60^0C hot water and detergent ○ We recommend that units consult their IPC teams on the management of items that cannot be adequately disinfected

Table 2: Delivery protocol for a pregnant patient with monkeypox

Mode of delivery	• Cesarean section (unless vaginal and anorectal lesions are absent AND vaginal and rectal MPXV-PCR swabs are negative) • PPE and IPC measures (see table 1)
Site of delivery	• Negative-pressure operating theatre
Anesthesia and surgical considerations	• Regional anesthesia preferred depending on clinical condition AND absence of suspected lesions on the back • Extended-spectrum antibiotics with cefazolin plus azithromycin • Preoperative skin antisepsis with povidone-iodine is probably safer than chlorhexidine-alcohol • Nonadhesive surgical drapes if extensive abdominal rash present • Consent patient for placental histology • Consent patient for MPXV-PCR of the following specimens (collected at delivery): amniotic fluid, cord blood, placenta, vaginal swab and rectal swab
Postpartum care	• Management of neonate (see table 3) • LMWH not contraindicated for postpartum thromboprophylaxis in monkeypox • Consent patient for MPXV-PCR of expressed breastmilk • Complete WHO monkeypox case report form (available at: https://www.who.int/publications/i/item/WHO-MPX-Clinical_CRF-2022.3)

MPXV = monkeypox virus; LMWH = low molecular weight heparin

Table 3: Management of the neonate

General management	○ Neonatology team should be informed of all cases
Management of neonates delivered by cesarean section	○ **Low risk of vertically transmitted monkeypox infection** ○ No active treatment required ○ Monitor for skin, eye and mucous membrane lesions, irritability and poor feeding ○ Delay breastfeeding and skin-to-skin until the mother is deisolated
Management of neonates delivered vaginally (e.g., birth before arrival or precipitate labour in mothers with active or suspected monkeypox infection)	○ **High risk of vertically transmitted monkeypox infection** ○ Swabs of skin, oropharynx and rectum for MPXV-PCR ○ Consider empirical treatment with intravenous vaccinia immune globulin in consultation with neonatal and infectious disease specialists ○ Monitor for skin, eye and mucous membrane lesions, irritability and poor feeding ○ Consider re-uniting mother and baby if both are positive for monkeypox and encourage breastfeeding unless the mother has a monkeypox rash around the nipples

Table 4: Practical prescribing considerations for monkeypox therapy in pregnancy

<table>
<tr><th>Therapy</th><th>Dose</th><th>Obstetric precautions</th></tr>
<tr><td>Tecovirimat</td><td>600 mg oral twice/daily for two weeks</td><td>Beware the risk of QTc prolongation in pregnancy
Obtain an ECG before starting tecovirimat in pregnancy
Tecovirimat can cause prolongation of the QTc interval – this may trigger torsade de pointes (TdP)
TdP may be asymptomatic or fatal (ventricular fibrillation)
Women are at higher risk because the baseline QTc interval is longer in women than men (470 ms vs 450 ms)
Macrolides – specifically erythromycin – is a well-known drug-induced cause of prolonged QTc
Beware the possibility of TdP in a pregnant woman with monkeypox and PPROM receiving both tecovirimat and erythromycin</td></tr>
<tr><td>Vaccinia immune globulin intravenous (VIGIV)</td><td>6,000 units/kg IV infusion

<u>For patients >50kg</u><table><tr><td>Time</td><td>Infusion rate</td></tr><tr><td>0 min</td><td>0.5 ml/min</td></tr><tr><td>30 min</td><td>1.0 ml/min</td></tr><tr><td>45 min</td><td>1.5 ml/min</td></tr><tr><td>60 min</td><td>2.0 ml/min (max)</td></tr></table><u>For patients <50kg</u></td><td>Beware the patient with gestational or pre-existing diabetes mellitus
Maltose in VIGIV can interact with glucose monitoring systems resulting in falsely-high readings and inappropriate insulin administration
Glucose monitors and test strips using glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase methods <u>must not</u> be used for blood glucose monitoring (e.g., 7-point BSP) in pregnant women receiving VIGIV
Beware the risk of venous thromboembolism (VTE)</td></tr>
</table>

<table>
<tr>
<td></td>
<td>
<table>
<tr><td>Time</td><td>Infusion rate</td></tr>
<tr><td>0 min</td><td>0.01 ml/kg/min</td></tr>
<tr><td>30 min</td><td>0.02 ml/kg/min</td></tr>
<tr><td>45 min</td><td>0.03 ml/kg/min</td></tr>
<tr><td>60 min</td><td>0.04 ml/kg/min (max)</td></tr>
</table>
</td>
<td>

VIGIV is associated with a risk of VTE in non-pregnant patients – this iatrogenic risk is likely higher in pregnant women
Slow down the VIGIV infusion rates in pregnant women
Do not exceed 12,000 units/kg in patients with VTE risk
Consider concurrent LMWH in pregnant women with additional risk factors for VTE who are receiving VIGIV (personal opinion)

Beware the patient with allergies

VIGIV is a blood product and can cause potentially life-threatening hypersensitivity reactions (anaphylactic shock)
Check baseline BP, HR and temperature in <u>all</u> patients before starting VIGIV infusion
Consider CTG monitoring (depending on gestational age) in pregnant women receiving VIGIV or if a severe allergic reaction occurs

</td>
</tr>
</table>

QTc = heart-rate corrected QT interval; PPROM = preterm prelabor rupture of membranes; BSP = blood sugar profile; BP = blood pressure; HR = heart rate; LMWH = low molecular weight heparin; CTG = cardiotocogram

Box 2: Knowledge gaps and research priorities for monkeypox in pregnancy

Clinical features

• What is the impact of the timing of maternal monkeypox infection in each trimester of pregnancy on the rate of obstetric outcomes in a geographically diverse cohort?
  o Miscarriage
  o Stillbirth
  o Preterm births
  o Birthweight
  o Fetal growth restriction
  o Maternal morbidity (including psychological) and mortality
 	
• What is the rate of severe maternal infection (based on WHO clinical severity score or MPXV viral load assessment) and the impact of the severity of maternal infection on obstetric outcomes ?
  o What is the rate of asymptomatic or pauci-symptomatic infection ?
  o Do asymptomatic or pauci-symptomatic infections carry risks to the pregnancy ?

Maternal-fetal and neonatal transmission

• What is the risk of congenital infection?
  o What is the rate of vertical transmission?
  o In the event of fetal infection, what is the proportion of asymptomatic and symptomatic fetuses?
  o Does the risk of congenital monkeypox correlate with the severity of maternal disease?
  o Does detecting MPXV in semen carry any risk to the pregnancy?
 	
• What is the mechanism of vertical transmission of monkeypox?
  o Can MPXV be isolated from the placenta or other fetal tissues?
  o What is the sensitivity for the molecular detection of MPXV from amniotic fluid?
  o Is the detection of MPXV from amniotic fluid or fetal tissues only transient (as seen in Zika) ?
 	
• What is the risk of transmission during breastfeeding?

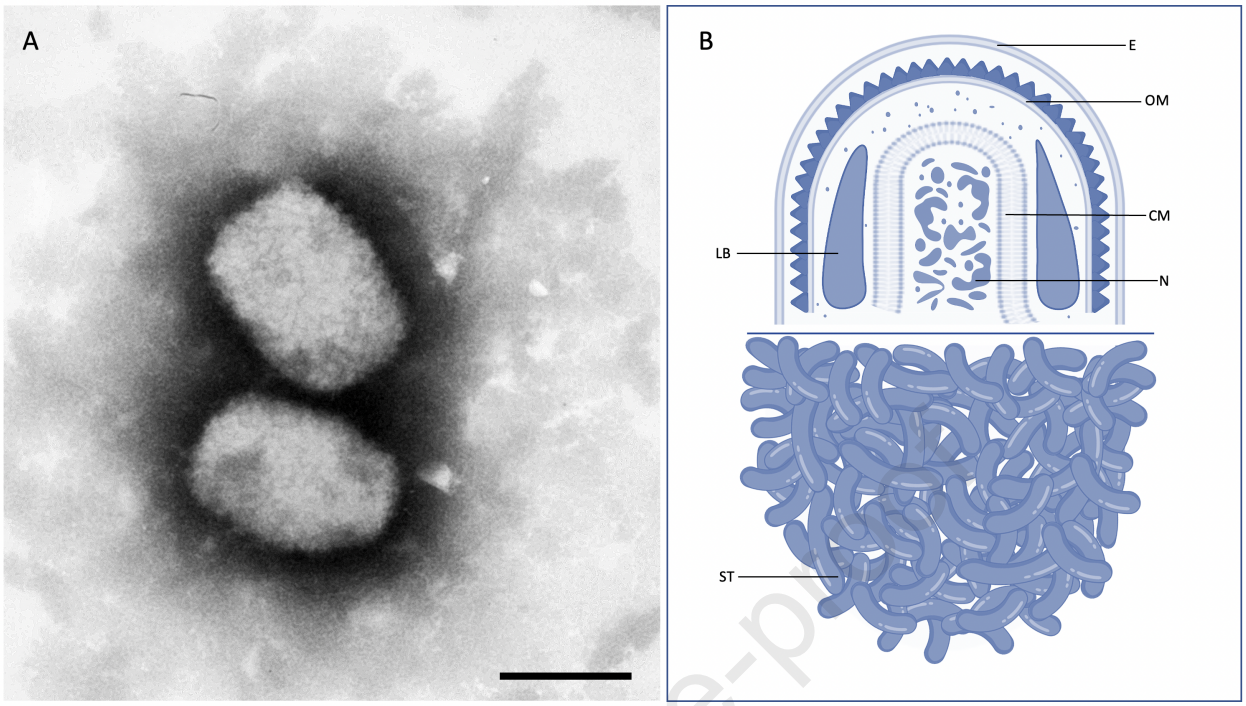
- Can MPXV be isolated from breastmilk?

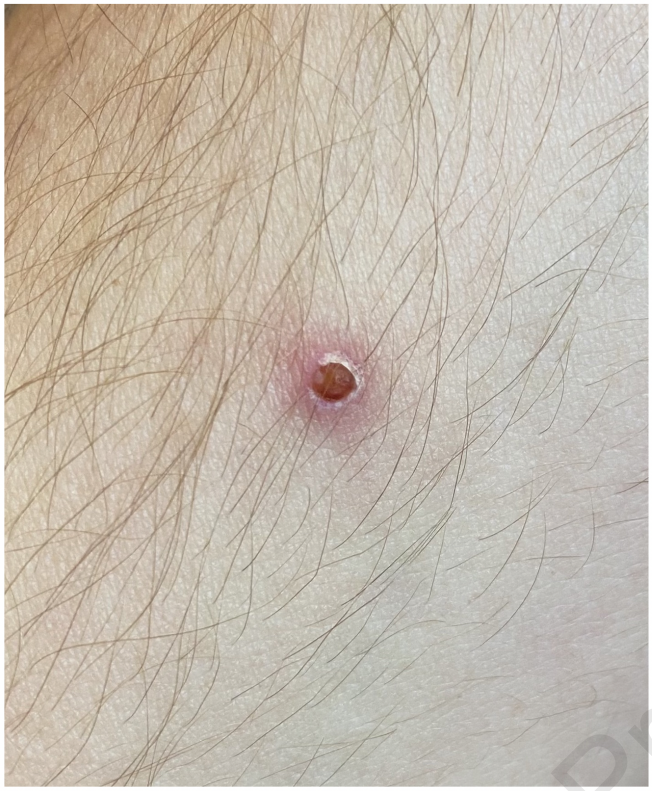
Therapeutics and vaccines

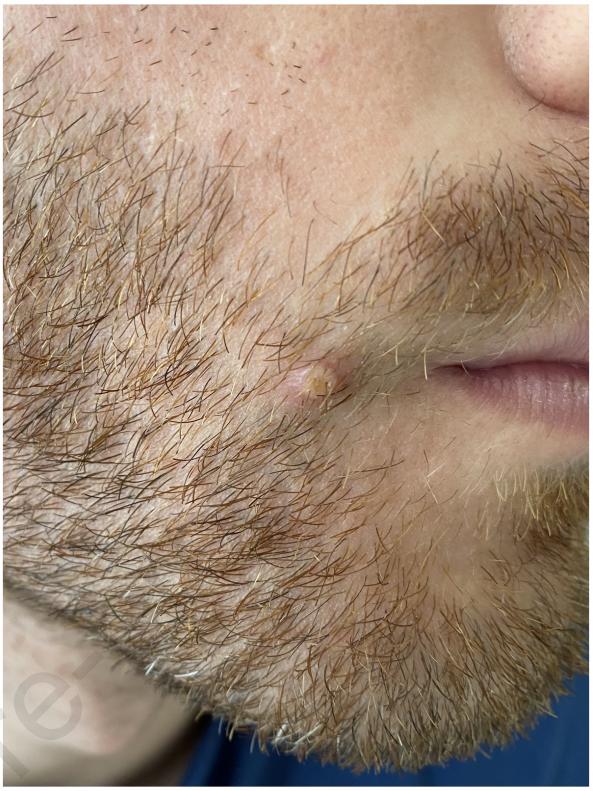
- What are the issues from the use of tecovirimat (and other new antivirals) in pregnancy?
  - Iatrogenic risks to mother and fetus
  - Does tecovirimat shorten the duration of illness and MPXV viral shedding in pregnancy?
  - Does tecovirimat reduce the risk of severe disease and mortality in pregnancy?

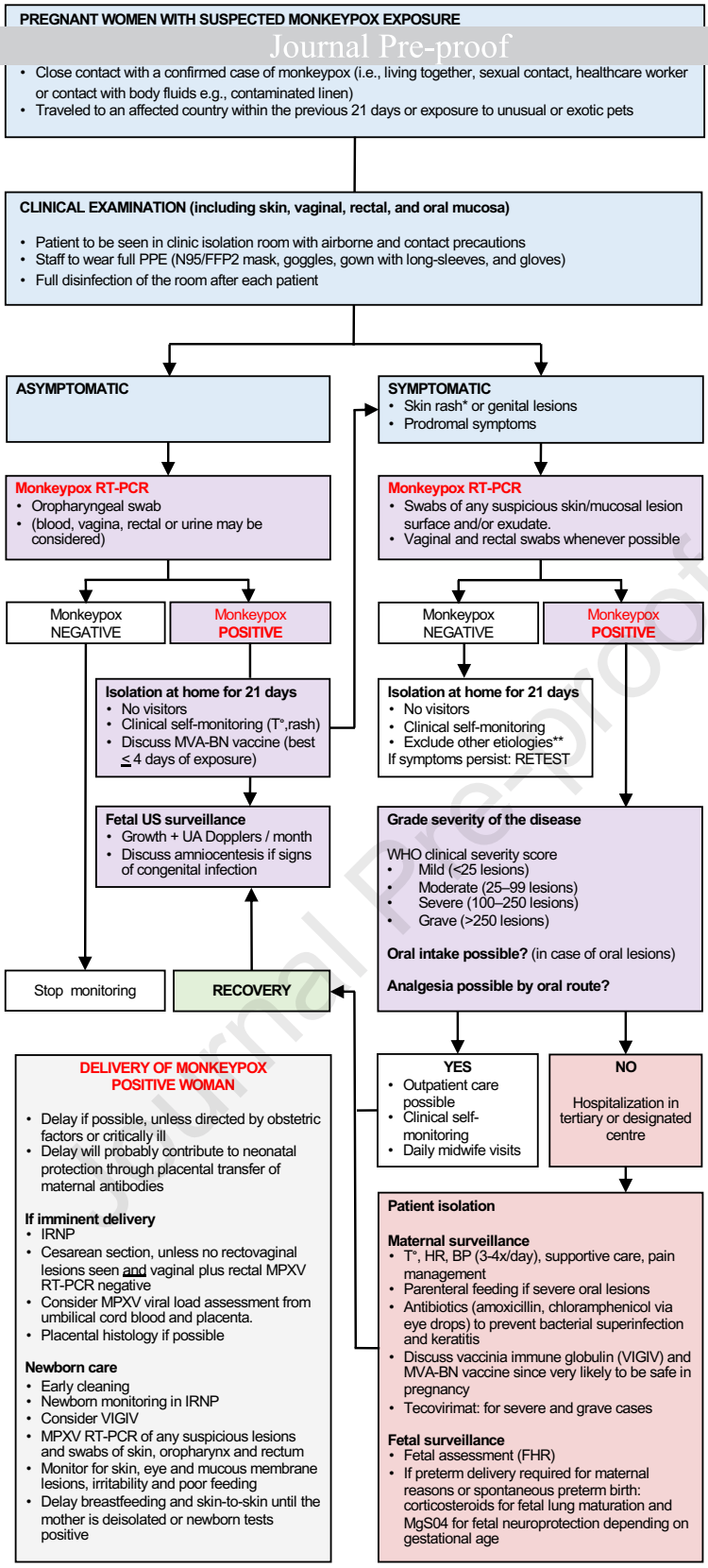
- What are the issues from the use of vaccinia immune globulin in pregnancy?

- What are the issues from the use of non-replicating (MVA-BN) and minimally replicating (LC16) orthopox vaccines in pregnancy?
  - Effectiveness in preventing infection
  - Maternal adverse reactions
  - Immunogenicity of the orthopox vaccine in pregnancy
  - Fetal risks from vaccine exposure, eg miscarriage and birth defects
  - Transplacental transfer of maternal antibodies derived from vaccination and protection of the fetus and neonate
  - Breastfeeding concerns, eg are the vaccine components detected in breastmilk and in the neonate?









*Higher suspicion if skin rash is concentrated over the genitals, face, and extremities. **PCR should be taken from a vesicle or genital lesion. We also suggest PCR for Herpes simplex (HSV), Varicella zoster (VZV) and Syphilis to rule out other causes of vesiculopustular rash in pregnancy.

MPXV: Monkeypox virus; **BP**: Blood pressure**; FHR** : Fetal heart rate**; HR**: Heart rate; **IRNP:** Isolation room with negative pressure; **IV**: Intravenous; **T°**: Temperature; **TOP**: Termination of pregnancy**; RT-PCR:** Real-time polymerase chain reaction**; US**: Ultrasound; **WG**: Weeks of gestation; **UA:** umbilical artery; **MgS04:** Magnesium sulphate