

A Primer on Monkeypox Virus for Obstetrician–Gynecologists

Diagnosis, Prevention, and Treatment

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Since May 2022, more than 6,900 cases of monkeypox virus infection have been reported in 52 countries. The World Health Organization is planning to rename the virus and its clades to reduce stigma. As of July 5, 2022, 556 cases have been reported in 33 U.S. states and the District of Columbia. The initial cases were travel-associated; however, person-to-person transmission is now occurring domestically. Close, sustained skin-to-skin contact, including during sexual activity, appears to be the primary mode of transmission. The risk of widespread community transmission remains low; however, rapid identification of monkeypox virus infection and isolation of affected individuals is critical to prevent further transmission. Most but not all cases have occurred in males; some infections have started with anogenital lesions and can be mistaken for common sexually transmitted infections. To facilitate rapid, accu-

rate diagnosis of monkeypox virus infection, obstetrician–gynecologists (ob-gyns) in the United States should ask about recent travel history and new ulcers or lesions and perform a thorough visual inspection of skin and mucosal sites (oral, genital, perianal area) in patients presenting with new rash. Obstetrician–gynecologists should become familiar with the appearance of monkeypox lesions and know whom to call to report a suspected case, how and when to test for monkeypox virus, and how to counsel patients. In the event of a suspected case, ob-gyns should follow infection-control guidelines to prevent transmission and make recommendations to prevent further community spread. This article outlines the diagnosis, prevention, and treatment of monkeypox virus infection, monkeypox virus infection during pregnancy, and implications for practicing ob-gyns in the United States.

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Monkeypox virus was named after it was first discovered in laboratory monkeys in 1958. However, there has been a recent call to rename the virus to reduce stigma, and the World Health Organization is planning to rename the virus and its clades.^{1,2} Monkeypox virus is an orthopoxvirus and exhibits features similar to smallpox or variola virus.^{3–6} Monkeypox virus has two different strains, the West African and the Congo Basin clades, with the latter associated with more severe illness and higher case fatality.^{3–5} The first human case of monkeypox virus infection was reported in 1970 in the Democratic Republic of Congo. Although monkeypox virus is endemic in several countries in Central and West Africa, recent cases have been linked to travel to countries where monkeypox virus does not naturally occur.^{3–5,7,8}

It has been nearly 20 years since a monkeypox virus outbreak occurred in the United States. In 2003, the first outbreak of human monkeypox virus outside of Africa was reported, linked to contact with infected prairie dogs. The prairie dogs acquired monkeypox virus after contact with small mammals imported from Ghana, where monkeypox virus is endemic, and passed the virus to humans interacting with them as pets.⁴⁻⁶ The 2003 introduction of monkeypox virus into the United States resulted in 47 cases in six states, all linked to animal contact.⁵ Until the current outbreak, only two additional cases of monkeypox virus infection were reported in the United States (in July and November 2021), both linked to travel to Nigeria.^{3,5}

As of July 5, 2022, 6,924 confirmed cases of monkeypox virus infection had been reported in 52 nonendemic countries, with the highest case counts in the United Kingdom, Spain, and Germany.⁸ On May 17, 2022, the first case in the United States of the West African strain of monkeypox virus infection was confirmed in a traveler who returned from Canada.⁹ As of July 5, 2022, 556 cases of the West African clade of monkeypox virus had been reported in 26 states and the District of Columbia; no deaths have been reported, and no cases have been reported among pregnant people.¹⁰ Although the initial cases were associated with travel outside the United States, person-to-person, community-acquired transmission has occurred, including transmission to women and transgender men.¹¹

The source of the current multinational outbreak has not yet been determined. Preliminary analyses of viral genomic sequences show similarities with those identified from Nigeria, suggesting that there were at least two instances in which monkeypox virus was introduced to nonendemic countries.^{3,4,11} The current cases have included uncharacteristic presentations of monkeypox virus infection; many of the initial patients presented with painful genital and perianal lesions, oral lesions, and proctitis in the setting of mild or no prodromal symptoms, linked to sexual activity between men.¹¹ However, as of July 5, 2022, seven cases of monkeypox virus infection have been reported in women and transgender men in the United States.^{10,11} Obstetrician-gynecologists (ob-gyns) need up-to-date information because they may be the first health care professionals to see individuals with symptoms of monkeypox virus infection, particularly if anal or genital lesions (which may be easily confused with common sexually transmitted infections) are present. In addition, orthopoxviruses pose unique concerns during pregnancy; although little is known about monkeypox virus infection and pregnancy,

prompt diagnosis, prevention, and treatment may reduce the risk of adverse outcomes.⁶

CLINICAL COURSE

The average time between contact with monkeypox virus and symptoms is 5–13 days, with a range of 4–17 days.^{7,12} The classic features of the infection include fever, lymphadenopathy, malaise, headache, and muscle aches. Lymphadenopathy may occur in the submandibular, cervical, axillary, or inguinal regions and may be unilateral or bilateral. Typically, a rash develops approximately 1–4 days after these prodromal symptoms, characterized as deep-seated, vesicular, or pustular, most often beginning centrally and spreading to the limbs. The rash can last 2–4 weeks, progressing through stages including macules, papules, vesicles, pustules, and eventually scabs and crusts.¹² The rash often can leave scars. The lesions are firm, well circumscribed, may be umbilicated or confluent, and may be in varied stages of progression at different sites.^{7,11,12} An example of the rash is provided in Figure 1. Additional photographs are available at: <https://www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-recognition.html>.

The distribution of lesions in the current outbreak is unusual. All patients thus far have exhibited a rash; however, the lesions often have begun in mucosal areas (eg, genital, perianal, oral mucosa) and localized to a specific body site.¹¹ The initial symptoms have included anorectal pain, tenesmus, and rectal bleeding associated with anogenital lesions.¹¹ Although most infections have been self-limited, several patients have required hospitalization for pain control of anogenital lesions.¹¹ The case fatality rate reported with the West African clade ranges from 1% to 11%.⁷

TRANSMISSION

Individuals with monkeypox virus infection should be considered contagious when symptoms occur, during the prodromal period, and, most importantly, while exhibiting the rash.¹¹⁻¹³ To minimize transmission, symptomatic individuals should be promptly isolated, cover any lesions, and wear a well-fitting mask if leaving isolation.¹³ Patients should avoid sex (oral, anal, vaginal), close contact, and sharing of towels, linens, sex toys, and toothbrushes.^{13,14} Patients are contagious until the scabs have crusted over and fallen off and a fresh layer of intact skin has formed underneath.¹¹⁻¹⁴ Monkeypox virus lesions can be confused with dermatologic conditions or sexually transmitted infections, including genital herpes, syphilis, lymphogranuloma venereum, varicella zoster, molluscum contagiosum, and chancroid.^{7,11,14} During pregnancy, monkeypox



Fig. 1. Photographs of the rash. Panels **A** and **B** show scattered papulovesicular lesions on the chest that were present 2 days before admission. The lesions measure 2 mm in diameter, are filled with clear fluid, and have surrounding erythema. Panel **C** shows a lesion on the right palm that was present at the time of admission. Panel **D** shows a papulovesicular lesion on the left second finger, which was one of the last skin lesions to develop, approximately 2 weeks after the onset of symptoms. Reprinted from Basgoz N, Brown CM, Smole SC, Madoff LC, Biddinger PD, Baugh JJ, Shenoy ES. Case 24–2022: a 31-year-old man with perianal and penile ulcers, rectal pain, and rash. *N Engl J Med* 2022;Jun 15. doi: 10.1056/NEJMcpc2201244. Copyright © 2022 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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virus infection may be confused with pruritic urticarial papules and plaques of pregnancy. Obstetrician-gynecologists should perform monkeypox virus testing if they have any clinical suspicion, particularly in the presence of risk factors such as recent travel or contact with an individual with known or suspected monkeypox virus infection.¹¹

EVALUATION OF INDIVIDUALS WITH SUSPECTED MONKEYPOX VIRUS INFECTION

Routine screening is not recommended for asymptomatic patients. If there is suspicion of monkeypox virus infection, ob-gyns should collect a recent travel history, asking specifically about countries where monkeypox virus infection has been reported.¹¹ For any patient with a rash or anogenital lesions, ob-gyns should inquire about close contact or sexual exposure to an individual known to have monkeypox virus

infection or anyone with a recent rash or anogenital lesions. A full-body skin examination, including visual inspection of the oral mucosa and genital and rectal areas, and evaluation of lymph node basins should be performed.¹¹

Patients who present with an unexplained fever, rash, or significant lymphadenopathy not otherwise explained should be isolated from others and placed in a separate room.^{11,15} Health care professionals have acquired monkeypox virus through close, sustained contact with a patient or contaminated fomites in the absence of appropriate personal protective equipment.^{16,17} Health care professionals who interact with the patient should follow standard precautions and wear appropriate personal protective equipment, including gown, gloves, eye protection (ie, goggles or a face shield that covers the front and sides of the face), and a National Institute for Occupational Safety

and Health–approved particulate respirator equipped with N95 filters or higher. Any activities with the potential to aerosolize particles (eg, intubation, extubation) should be performed in an airborne infection–isolation room.¹⁵ Because monkeypox virus can spread by fomites, infection-control practices must dictate how any contaminated bandaging, bedding, or clothing worn by the patient is handled.¹⁵

Obstetrician–gynecologists encountering a patient with suspected monkeypox virus infection should consult with their hospital infection-control specialists and public health authorities about diagnosis. Making the diagnosis of monkeypox virus infection is a two-step process requiring initial identification of an orthopoxvirus. If an orthopoxvirus is confirmed, specimens are sent for monkeypox virus–specific testing.^{7,9,11} Multiple samples should be collected, ideally from different lesions (two to three from different areas of the body or of different appearance), for polymerase chain reaction testing. Lesion swabs or crusts from lesions are acceptable specimen types.¹⁸

Given the absence of other circulating orthopoxviruses in the United States, clinicians should not wait for confirmation of monkeypox virus infection before initiating infection-control procedures and preventive strategies and considering treatment options once an orthopoxvirus infection is confirmed.¹¹ Co-infection with sexually transmitted infections has been reported; a diagnosis of a sexually transmitted infection does not preclude testing for monkeypox virus infection and vice versa.¹¹

MONKEYPOX VIRUS INFECTION AND PREGNANCY

Information about monkeypox virus infection during pregnancy is limited.⁶ Five laboratory-confirmed cases have been reported in the literature; four were identified in the Democratic Republic of the Congo and one in Zaire (Table 1).^{19,20} Among these cases, three pregnancies resulted in fetal loss, including two spontaneous abortions and one stillbirth. Evaluation of the fetal remains demonstrated a maculopapular rash, hepatomegaly, peritoneal effusions, and hydrops fetalis. Monkeypox virus infection was confirmed by polymerase chain reaction testing in fetal tissues and in the placenta, with high viral loads detected in several fetal tissues.¹⁹ An additional mild case of maternal monkeypox virus infection resulted in the live birth of a reportedly healthy neonate at term, without evidence of congenital monkeypox virus infection.¹⁹ The fifth case was detected in 1983 in Zaire. In this case, maternal monkeypox virus infection was diagnosed in the second trimester

of pregnancy, followed almost 6 weeks later by the preterm birth of a neonate with a generalized rash suggestive of congenital monkeypox virus infection. The infant subsequently died from malnutrition at 6 weeks of age; no neonatal laboratory testing for monkeypox virus infection was available, but congenital syphilis was ruled out.²⁰

It is not known whether pregnant people are more susceptible to monkeypox virus infection or whether the infection is more severe during pregnancy.⁶ Smallpox virus, a similar orthopoxvirus, is known to be associated with more severe illness during pregnancy, with a higher case fatality rate and a greater risk of hemorrhagic complications.^{6,21,22} Adverse pregnancy outcomes have been associated with several orthopoxviruses, including monkeypox virus infection during pregnancy.^{19–24} Miscarriage and stillbirth have been reported with monkeypox virus, smallpox virus, cowpox virus, and vaccinia virus infection.^{19–24} Congenital infection has been reported with four orthopoxviruses: monkeypox virus, smallpox virus, cowpox virus, and vaccinia virus.^{19–24} Preterm birth has been reported in a single case of monkeypox virus infection but has also been reported with maternal smallpox virus and vaccinia virus infection.^{19–24} The frequency of and risk factors for adverse outcomes associated with monkeypox virus infection during pregnancy are not known.

TREATMENT

Monkeypox virus infection can be self-limited; however, certain populations are at risk for severe disease and should be considered for treatment. This includes all pregnant people with monkeypox virus infection regardless of trimester of infection, people who are breastfeeding, and people with oral, ocular, genital, or anal lesions.²⁵

Although there are no specific treatments for monkeypox virus infection, two antivirals and vaccinia immune globulin are available from the Strategic National Stockpile under expanded access investigational new drug protocols held by the Centers for Disease Control and Prevention (CDC).²⁵ Tecovirimat is approved by the U.S. Food and Drug Administration (FDA) for the treatment of smallpox virus infection and may prove beneficial for monkeypox virus infection. It is available in oral and intravenous formulations (FDA. Tecovirimat package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208627s000lbl.pdf). Both forms have been used to treat patients during the current outbreak in the United States.^{7,11,25} There are no human data on the use of tecovirimat during pregnancy; reproductive development and toxicity are

Table 1. Cases of Monkeypox Virus Infection During Pregnancy

Author, Year, Location	Laboratory Test (PCR)	No. of Monkeypox Virus Lesions	Pregnancy Outcome	Gestational Age at Diagnosis; Time from Illness Onset to Pregnancy Outcome	Other Clinical Findings
Jezek and Fenner, 1983, North Zaire	Monkeypox virus isolated from maternal vesicle fluid	n/a	Preterm birth of female neonate “at the beginning of 7th month”; neonatal rash clinically consistent with congenital monkeypox virus infection; neonatal death at 6.5 wk of age from “malnutrition”	Approximately 5.5 mo; 6 wk	Maternal: initially presented with fever followed by rash the next day; serum test negative for syphilis Neonate: birth weight less than 1,500 g; laboratory samples lost; scabs reported on skin 2 wk after birth
Mbala et al, 2017, Democratic Republic of the Congo	Yes Yes Yes	76 1,135 113	Spontaneous abortion Spontaneous abortion Stillbirth; congenital monkeypox virus infection	1 st trimester; 14 d 1 st trimester; 24 d 18 wk; 21 d	Congo Basin strain Congo Basin strain Congo Basin strain; viral load increased with onset of fever and lack of fetal movement; co-infection with malaria; virus isolated in fetal tissue and placenta
	Yes	16	Full-term live birth	14 wk; 6 mo	Congo Basin strain

PCR, polymerase chain reaction; n/a, not available.

limited to animal studies. No fetal toxic effects were observed in mice studies using oral tecovirimat at levels approximately 23 times higher than the recommended human dose, nor in rabbits at levels less than the recommended dose during the period of organogenesis (FDA. Tecovirimat package insert.). It is not known whether treatment with tecovirimat during pregnancy prevents congenital monkeypox virus infection.

Cidofovir, an antiviral approved by the FDA for the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome (AIDS), is available for treatment of orthopoxviruses in an outbreak setting.²⁵ In animal studies, cidofovir has been associated with embryotoxicity and teratogenicity and was formerly categorized as FDA Category C. This indicates that animal-reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but the potential benefits may warrant use of the drug in pregnant women despite potential risks (FDA. Cidofovir package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/020638s003lbl.pdf).

Brincidofovir, an antiviral approved by the FDA for the treatment of smallpox virus infection, is not currently available in the Strategic National Stock-

pile.²⁵ Pregnancy testing is recommended before use of this drug. Brincidofovir studies in pregnant rats and rabbits demonstrated embryo–fetal toxicity and structural malformations at doses less than the expected human dose. Therefore, alternative therapy is recommended to treat smallpox virus infection during pregnancy. Individuals of childbearing potential should avoid becoming pregnant and use effective contraception during treatment and for at least 2 months after the last dose. Male sexual partners of reproductive-aged females should use condoms during treatment and for at least 4 months after the last dose (FDA. Brincidofovir package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf).

Lastly, vaccinia immune globulin intravenous is licensed by the FDA for the treatment of complications due to vaccinia vaccination and is also available for the treatment of orthopoxviruses in an outbreak setting.²⁵ No human or animal data are available for vaccinia immune globulin intravenous during pregnancy; however, other immunoglobulins have been widely used in pregnancy without negative side effects. Vaccinia immune globulin intravenous was formerly categorized as FDA Category C because of the lack of data (FDA. Vaccine Immune Globulin

Intravenous package insert. <https://www.fda.gov/media/78174/download>). For access to any of these treatment options, clinicians should contact their state or territorial health departments, which will facilitate a request through the CDC and the Strategic National Stockpile.²⁵

PREVENTION

Primary prevention of monkeypox virus infection involves isolating individuals with infection from other people and their pets, avoiding close contact and sexual activity with people with infection, and postexposure vaccination.^{11,13–15} Any close contact, including sexual contact, with an individual known or suspected to have monkeypox virus infection should be avoided until all lesions have resolved, the scabs have fallen off, and a fresh layer of intact skin has formed.^{11,13–15} Given the known incubation period for monkeypox virus, individuals identified as close contacts of people with monkeypox virus infection should be traced, reported to the health department, and advised to monitor for signs and symptoms for 21 days. Contacts who remain asymptomatic can engage in routine activities.²⁶

POSTEXPOSURE PROPHYLAXIS

The CDC has tools to assess the risk of monkeypox virus infection and recommends postexposure vaccination for specific risk exposures or risk factors.^{26–28} Eligible contacts are offered postexposure prophylaxis with one of two vaccines. If given within 4 days of exposure, the vaccine is likely to prevent monkeypox virus infection. If given 4–14 days postexposure, vaccination is likely to reduce symptoms but may not prevent disease.²⁷ ACAM2000 is a replication-competent vaccinia virus vaccine that has been approved by the FDA for the prevention of smallpox virus infection. It has not been studied during pregnancy; however, live vaccinia virus vaccines can cause fetal vaccinia and fetal death (FDA. ACAM2000 package insert. <https://www.fda.gov/media/75792/download>). Pregnant women who are close contacts of vaccinees who receive a replication-competent vaccinia vaccine may be at increased risk for these complications, because infectious vaccinia virus is shed from the vaccine site lesion and can be transmitted to close contacts (FDA. ACAM2000 package insert. <https://www.fda.gov/media/75792/download>). JYNNEOS (also known as Imvamune or Imvanex) is an attenuated live-virus vaccine that has been approved by the FDA for the prevention of smallpox virus and monkeypox virus infection. The vaccine was evaluated in four developmental toxicity studies conducted in female rats and rabbits. These animal studies revealed no evidence of harm to the fetus (FDA. JYNNEOS

package insert. <https://www.fda.gov/media/75792/download>). Because the vaccine is a nonreplicating vaccine, it is the preferred vaccine for pregnant individuals.²⁸ Pregnancy is not a contraindication to postexposure prophylaxis with vaccination if the individual is otherwise eligible.²⁸

PREEXPOSURE PROPHYLAXIS

The attenuated live-virus vaccine and replication-competent vaccine are also available for preexposure prophylaxis.²⁹ Currently, the Advisory Committee on Immunization Practices recommends vaccination for certain people at risk for exposure to orthopoxviruses.²⁹ Individuals whose jobs may expose them to monkeypox virus, including laboratory personnel and health care workers who administer a replication-competent vaccinia virus vaccine or anticipate caring for many patients with monkeypox virus infection, are eligible for either vaccine.²⁹ Routine immunization of all health care workers is not currently recommended. The attenuated live-virus vaccine is the preferred vaccine for preexposure prophylaxis of pregnant individuals who are eligible, and pregnancy is not a contraindication to preexposure prophylaxis. According to Advisory Committee on Immunization Practices recommendations, the replication-competent vaccinia virus vaccine is contraindicated during pregnancy and while breastfeeding for preexposure prophylaxis.²⁹

SURVEILLANCE OF MONKEYPOX VIRUS INFECTION CASES IN THE UNITED STATES

Although monkeypox virus infection is not currently a nationally notifiable disease, a standardized case definition is available to track monkeypox virus infection and cases are voluntarily reported to the CDC. Pregnancy status is part of case identification; monkeypox virus testing has been performed for several pregnant people. If cases were to occur in pregnant people, the CDC may activate SET-NET (Surveillance of Emerging Threats to Mothers and Babies Network), a surveillance system established to capture information associated with maternal infections.³⁰

CONCLUSION

Monkeypox virus infection has been reported in many nonendemic countries, including the United States. Cases have been linked to international travel and close, sustained contact, including during sex. Most ob-gyns have never seen a case of monkeypox virus infection and may not be aware of testing, treatment, or preexposure or postexposure vaccine options. Obstetrician-gynecologists are likely to be the first providers to see individuals with monkeypox virus infection and may receive questions from their patients.

Obstetrician–gynecologists need up-to-date information to promptly diagnose monkeypox virus infection; treat patients at-risk for severe disease, including pregnant people; and prevent further spread of the infection.

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