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Perspective

Mpox in Pregnancy — Risks, Vertical Transmission, Prevention, and Treatment

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The alarming surge in human-to-human transmission of monkeypox virus (MPXV) infections, particularly in high-risk, sexually active, and reproductive-age populations, along with the known association between MPXV infection and adverse obstetrical outcomes, highlights the urgent need for data to enhance our understanding and mitigate the risks of MPXV infection during pregnancy.

Mpox is a zoonotic disease caused by MPXV, a DNA virus of the orthopoxvirus genus in the family poxviridae, and is closely related to smallpox. Although MPXV was discovered in 1958, the first human case was reported in 1970 in the Democratic Republic of Congo (DRC). The virus has two clades: clade I (formerly Congo Basin clade) and clade II (formerly West African clade, now subdivided into IIa and IIb). Clade I is more virulent, with a case fatality ratio as high as 10%, as compared with 0 to 3.6% for clade II. Mpox data from the DRC reported to the World Health Organization (WHO) between January 1 and May 26, 2024 (N=7851) indicate that the case fatality ratio among children under 1 year of age is 8.6%, as compared with 2.4% among persons 15 years of age or older. Furthermore, people living with HIV and low CD4 counts may face a case fatality ratio greater than 10%.

Historically, mpox cases have predominantly arisen from zoonotic spillover in Central and West African countries, where MPXV circulates among wild rodents and nonprimate hosts. In 2022, a human clade IIb outbreak linked to sexual transmission led to a global epidemic, with a case fatality ratio of less than 0.2%, primarily affecting men who have sex with men. The outbreak was controlled by vaccination of high-risk groups.

Recent reports have raised concerns about outbreaks of the more lethal MPXV clade I in the DRC. In 2023, more than 12,000 cases and 600 deaths were reported to the WHO. Between September 2023 and January 2024, our group, the Mpox Research Consortium (MpoxReC; for a complete list of investigators and collaborators, see the Supplementary Appendix, available at NEJM.org), documented a substantial outbreak of

Proposed Research Agenda for Mpox in Pregnant or Breast-Feeding Persons.*

Key Research Area	Objectives	Specific Aims and Approach	Anticipated Outcomes
Risk factors and transmission dynamics (epidemiology)	Investigate transmission patterns of MPXV (clades I and II) in the context of pregnancy and breast-feeding.	Conduct epidemiologic studies in mpox-affected regions focused on infection rates and severity among pregnant and breast-feeding persons. Assess the impact of sexual transmission on MPXV spread in high-risk populations. Identify risk factors for MPXV acquisition in pregnant women using surveys and focus-group discussions; study associations with other sexually transmitted infections.	Improved understanding of transmission dynamics and impact of clades I and II on pregnancy and breast-fed infants
Vertical transmission mechanisms	Understand the mechanisms of vertical MPXV transmission, analyze the effect of gestational age on vertical transmission risk and severity of fetal or newborn disease; and identify critical windows for intervention.	Use animal models such as macaques to investigate the pathways of vertical transmission by gestational age. Analyze clinical samples from infected pregnant people and their offspring. Conduct antibody-based and molecular analyses to detect MPXV in pregnant persons, placentas, and fetuses; determine viral load; and identify dissemination patterns. Conduct prospective fetal ultrasonography to evaluate fetal growth and describe potential fetal abnormalities related to maternal MPXV infection. Evaluate breast-milk samples from infected breast-feeding persons to detect MPXV. Investigate relationship between transplacental transfer of maternal MPXV antibodies and vertical transmission of MPXV.	In-depth knowledge of the mechanisms of vertical transmission and critical intervention periods
Clinical outcomes and pregnancy complications	Document and analyze pregnancy outcomes in infected persons.	Conduct cohort studies of pregnant persons with mpox to assess maternal morbidity and mortality and pregnancy outcomes, including miscarriage, stillbirth, and neonatal health. Conduct prospective cohort studies in breast-feeding persons with confirmed MPXV to track infant outcomes.	Improved understanding of clinical outcomes and complications
Vaccine effectiveness and safety in pregnancy	Evaluate the safety and effectiveness of the MVA-BN vaccine in pregnant and breast-feeding persons.	Conduct trials to assess the effectiveness, immunogenicity, and safety profile of MVA-BN and candidate mRNA vaccines in pregnant and breast-feeding women. Evaluate the effect of maternal vaccination on vertical transmission. Monitor vaccinated pregnant and breast-feeding women and their offspring for pregnancy complications and other adverse events.	Robust evidence on the safety and efficacy of vaccination in pregnant and breast-feeding women
Antiviral treatment evaluation	Determine the pharmacokinetics, safety, and efficacy of tecovirimat and other antiviral therapies in pregnant and breast-feeding women with MPXV infection.	Conduct trials to investigate pregnancy-specific outcomes with tecovirimat treatment. Conduct pharmacokinetics and safety studies in pregnant and breast-feeding persons. Evaluate the effect of maternal treatment on vertical transmission risk.	Robust evidence for tecovirimat treatment in pregnant and breast-feeding women
Community engagement, education, and guideline development	Raise awareness and educate communities about the risks of mpox during pregnancy and breast-feeding and available preventive measures. Develop evidence-based guidelines for prevention and treatment of mpox in pregnant and breast-feeding women.	Investigate mpox vaccine acceptance and develop targeted communication campaigns to inform pregnant women about mpox risks and the importance of vaccination and early treatment. Partner with local health organizations to distribute educational materials and conduct workshops.	Enhanced public health strategies and community awareness to prevent pregnancy complications from mpox Guidelines for managing mpox in pregnant and breast-feeding women

* MPXV denotes monkeypox virus, MVA-BN Modified Vaccinia Ankara by Bavarian Nordic, and RT-PCR real-time polymerase chain reaction.

241 clade I cases in Kamituga, a gold-mining town in eastern DRC, affecting a highly mobile population of migrant workers. Genomic analyses identified a new mutation pattern in the isolated MPXV, now considered a distinct clade I strain with the proposed designation Ib. Among 108 patients with MPXV infection confirmed by real-time polymerase chain reaction (RT-PCR), the median age at infection was 22 years; 51.9% of patients were female, and 29.0% were sex workers, which suggests sexual transmission.[1] Alarmingly, infections have now been reported in Rwanda, Uganda, Burundi, and Kenya. Given this recent upsurge, the WHO declared mpox a Public Health Emergency of International Concern on August 14.

Historical data on smallpox during pregnancy reveal high rates of miscarriage, premature birth, and maternal death. In 15 studies involving 830 pregnant patients with smallpox, 331 (39.9%) had a miscarriage or premature birth; of 1074 pregnant patients in 16 studies, 368 died (case fatality ratio, 34.3%).[2] The limited available data suggest that mpox, like smallpox, increases the risks of severe maternal disease, miscarriage, and stillbirth. A 2024 systematic review of seven studies identified 32 pregnant women with clade IIb MPXV infection between 6 and 31 weeks of gestation.[3] Of the 12 pregnancies with reported gestational outcomes, half resulted in intrauterine fetal demise.

Like smallpox, MPXV can be transmitted from mother to fetus, with high viral loads (10^6 copies per milliliter in one case) found within fetal and maternal–fetal interface tissues, possibly contributing to pregnancy loss.[3] The potential for intrauterine transmission is further supported by data from nonhuman primates: a macaque model showed vertical transmission 6 to 14 days after infection, followed shortly by fetal demise.[4] Transmission from breast-feeding mothers with mpox to their infants can also occur, potentially by means of close contact. Whether MPXV is present in breast milk is unknown; breast milk from one MPXV-infected woman tested negative for MPXV DNA on PCR.[5] Outcomes were reported on three breast-feeding infants in studies of MPXV-infected mothers; all were infected, and one died.[3]

Because of the broad cross-immunity observed within the orthopoxvirus family, the WHO Strategic Advisory Group of Experts on Immunization recommends administering one of two smallpox vaccines for mpox prevention: the Modified Vaccinia Ankara vaccine, developed by Bavarian Nordic (MVA-BN), or the LC16m8 vaccine, developed by KM Biologics in Japan. The MVA-BN vaccine, containing live, nonreplicating virus, is marketed under various names — JYNNEOS in the United States, Imvanex in the European Union, and Imvamune in Canada — and is approved (including in the DRC) for persons 18 years of age or older who are at risk for mpox, including pregnant or breast-feeding women. Developmental toxicity studies of MVA-BN in female rats and rabbits have revealed no harm to fetuses. The LC16m8 vaccine, approved in Japan and the DRC for adults and children, is typically contraindicated for immunocompromised patients and during pregnancy because it contains a replicating attenuated virus. However, since both vaccines' efficacy was extrapolated from the neutralizing antibody levels required for smallpox, clinical trials are needed to confirm their effectiveness in preventing clade I and clade II MPXV infections, particularly in high-risk groups including pregnant women.

In the United States, the antiviral agent tecovirimat is approved by the Food and Drug Administration for smallpox and available for treating severe mpox under an Expanded Access Investigational New Drug authorization from the Centers for Disease Control and Prevention (CDC). Although no pharmacologic data related to pregnancy or breast-feeding in humans exist, no embryotoxic or teratogenic effects were found when tecovirimat was administered to mice and rabbits at doses approximately 23 times the recommended human dose. Tecovirimat was detected in animal breast milk, but whether it crosses into human breast milk or the placenta is unknown. Because of the increased risk of severe disease during pregnancy and the possibility of severe infection in newborns, tecovirimat has been recommended in the United States as therapy for MPXV-infected persons who are pregnant or breast-feeding. In a study including 23 U.S. pregnant women with mpox, 11 received tecovirimat (including first-trimester use) and no medication-related adverse events were reported.[5]

Tecovirimat can be obtained from the CDC primarily for enrollees in the STOMP trial funded by the National Institutes of Health and the National Institute

of Allergy and Infectious Diseases (NIH/NIAID), which permits recruitment of pregnant and breast-feeding persons.

The PALM007 trial was launched in the DRC in partnership with the NIH/NIAID and the DRC's National Institute for Biomedical Research to evaluate tecovirimat's safety and efficacy in 600 children and adults, including pregnant women, with laboratory-confirmed MPXV. An NIH/NIAID press release on preliminary results was posted on August 15, 2024: though the study didn't meet the primary end point of statistically significant improvement in the time to lesion resolution, there was no difference from the placebo control in terms of adverse events. However, additional analyses are planned, and other trials are evaluating tecovirimat use for mpox in the United States (STOMP), Canada and the United Kingdom (PLATINUM), and Switzerland and Brazil (UNITY), some of which allow enrollment of pregnant or lactating persons. Since the PALM007 trial enrolled only 11 pregnant women, it will provide limited information about pregnancy outcomes. Larger studies are necessary to evaluate tecovirimat's safety during pregnancy and assess pregnancy-specific outcomes.

The MpoxReC has launched an mpox research program, including evaluating the accuracy of available diagnostic tools for MPXV (clades I and II), identifying MPXV reservoirs, and assessing the clinical efficacy of existing vaccines and therapeutics. The table outlines a pregnancy-focused research agenda aimed at improving our understanding of epidemiologic factors, transmission mechanisms, clinical outcomes, and the effectiveness of vaccines and antivirals. Such data are urgently needed to inform evidence-based clinical guidelines and public health policies regarding MPXV infection during pregnancy.

Disclosure forms provided by the authors are available at NEJM.org.

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