Mpox Virus in Pregnancy, the Placenta, and Newborn

An Emerging Poxvirus With Similarities to Smallpox and Other Orthopoxvirus Agents Causing Maternal and Fetal Disease

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• ***Context.***—**Before its eradication, the smallpox virus was a significant cause of poor obstetric outcomes, including maternal and fetal morbidity and mortality. The mpox (monkeypox) virus is now the most pathogenic member of the *Orthopoxvirus* genus infecting humans. The 2022 global mpox outbreak has focused attention on its potential effects during pregnancy.**

Objective.—**To understand the comparative effects of different poxvirus infections on pregnancy, including mpox virus, variola virus, vaccinia virus, and cowpox virus. The impact on the pregnant individual, fetus, and placenta will be examined, with particular attention to the occurrence of intrauterine vertical transmission and congenital infection.**

Data Sources.—**The data are obtained from the authors' cases and from various published sources, including early historical information and contemporary publications.**

Conclusions.—**Smallpox caused maternal and perinatal death, with numerous cases reported of intrauterine transmission. In endemic African countries, mpox has also affected pregnant individuals, with up to a 75% perinatal case fatality rate. Since the start of the 2022 mpox outbreak, increasing numbers of pregnant women have been infected with the virus. A detailed description is given of the congenital mpox syndrome in a stillborn fetus, resulting from maternal-fetal transmission and placental infection, and the potential mechanisms of intrauterine infection are discussed. Other poxviruses, notably vaccinia virus and, in 1 case, cowpox virus, can also cause perinatal infection. Based on the historical evidence of poxvirus infections, mpox remains a threat to the pregnant population, and it can be expected that additional cases will occur in the future.**

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Mpox, formerly referred to as *monkeypox*, is a potentially life-threatening infection whose prevalence and geographic distribution in endemic African countries has been increasing since the 1970s. From a public health and medical standpoint, the mpox virus (MPV) is currently the most important member of the *Orthopoxvirus* genus, a group of related viruses in the family Poxviridae and subfamily Chordopoxvirinae. It is a viral zoonosis endemic in Central and West Africa and is responsible for human disease with symptoms similar to smallpox. Unfortunately, it has largely been ignored by the medical and public health communities until recently.[1] As a consequence, its epidemiology, ecology, and pathophysiology remain largely unknown.

The ongoing outbreak of mpox was first confirmed on May 6, 2022, with the primary group of cases identified in the United Kingdom. The first outbreak case was identified in a person with a travel history linked to Nigeria, where the disease is endemic. Since early May 2022, cases of mpox have been reported from multiple countries where the virus has not been endemic.[2] Following its identification from 12 countries across the world, the World Health Organization (WHO) declared the outbreak a public health emergency of international concern on July 23, 2022, and the US Department of Health and Human Services declared mpox a public health emergency on August 4, 2022.[3,4] As of February 15, 2023, there were 30 193 cases of mpox in the United States, with 32 deaths.[5] In the United States, 99% of infected persons have been males, and 94% have reported male-to-male sexual or intimate contact.[6–8] Despite the preponderance of MPV infections in males, cases have been

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reported in women, and there has been an intense concern for pregnant individuals acquiring the infection.[9–16]

Smallpox is also caused by an orthopoxvirus, the variola virus (VARV), which before its eradication in 1977, had caused extensive morbidity and mortality among infected pregnant people and their fetuses. During pregnancy, smallpox had a case fatality rate (CFR) estimated at greater than 30%.[17] Because of its historical significance, smallpox is the most widely known orthopoxvirus. Still, other members of this genus have also infected pregnant people and been responsible for maternal illness and fetal death. Determining the historical impact of smallpox and other orthopoxviruses on maternal and fetal health is confounded by a few key issues. Case series captured in the scientific literature span the 19th and 20th centuries, representing a time of evolving obstetric knowledge and population vaccination status. There were at least 2 smallpox strains that imparted different levels of disease severity and complicated comparisons of outcomes across different cohorts. Our knowledge of strains and variants for other orthopoxviruses and how these might differentially impact pregnancy health is minimal. Nevertheless, they may provide relevant information about poxvirus infections in pregnancy.

The 2022 mpox outbreak has focused attention again on poxviruses in general, specifically the MPV. However, most health care personnel have not previously had the opportunity to become familiar with aspects of their epidemiology, diagnosis, and treatment. Following the eradication of VARV, the most pathogenic orthopoxvirus that infects humans is MPV. This communication will examine the effects of orthopoxvirus infections, including not only mpox but also smallpox, vaccinia, and others, occurring during pregnancy. It is hoped that reviewing the literature related to infection from these viruses in pregnancy will assist in developing basic conclusions as to the potential impact of MPV on pregnant persons, the placenta, and fetus.

SMALLPOX

Smallpox, caused by VARV, is a member of the *Orthopoxvirus* genus and was one of the most devastating diseases in the history of humanity. Recorded historically for more than 3000 years, smallpox resulted in hundreds of millions of deaths and an uncountable number of persons with permanent sequelae and disfigurement. An intense global program coordinated by the WHO eventually eliminated natural infections in 1977, becoming the first and only human infectious disease to be eradicated.[18] Smallpox had a strict human host range with no animal reservoir, aiding its eradication. The wealth of literature on smallpox in pregnancy and the clinical features of the disease might help inform clinical care and research to understand the impact of a related orthopoxvirus such as MPV on the pregnant individual, placenta, and fetus.

Smallpox was acquired by inhaling large, virus-containing airborne droplets from an infected individual's coughing or sneezing. The incubation period was approximately 12 days (7–19 days), and the first symptoms were fever, malaise, headaches, back pain, and abdominal pain. Typically, 2 to 3 days after the initial symptoms, a rash formed in the mouth, throat, face, and arms that would then spread to the trunk and legs. Smallpox lesions eventually transformed into pustules and sores that left scars.

There were several clinical forms of smallpox caused by the VARV strain variola major, including (1) ordinary smallpox with a CFR of approximately 62% in unvaccinated and 26.3% in vaccinated persons; (2) modified-type smallpox in vaccinated individuals (more rapid crusting of lesions); (3) flat-type (malignant) smallpox (more common in children, intense "toxemia") and fatal in 96.5% of unvaccinated and 66.7% of vaccinated persons; and (4) hemorrhagic-type smallpox, which was characterized by a shorter prodrome, more severe symptoms, bleeding diathesis, and death early in the disease course with a CFR of 100% in all infected individuals. Infection with the VARV strain variola minor (alastrim) produced milder symptoms and a CFR of approximately 1%.[18,19]

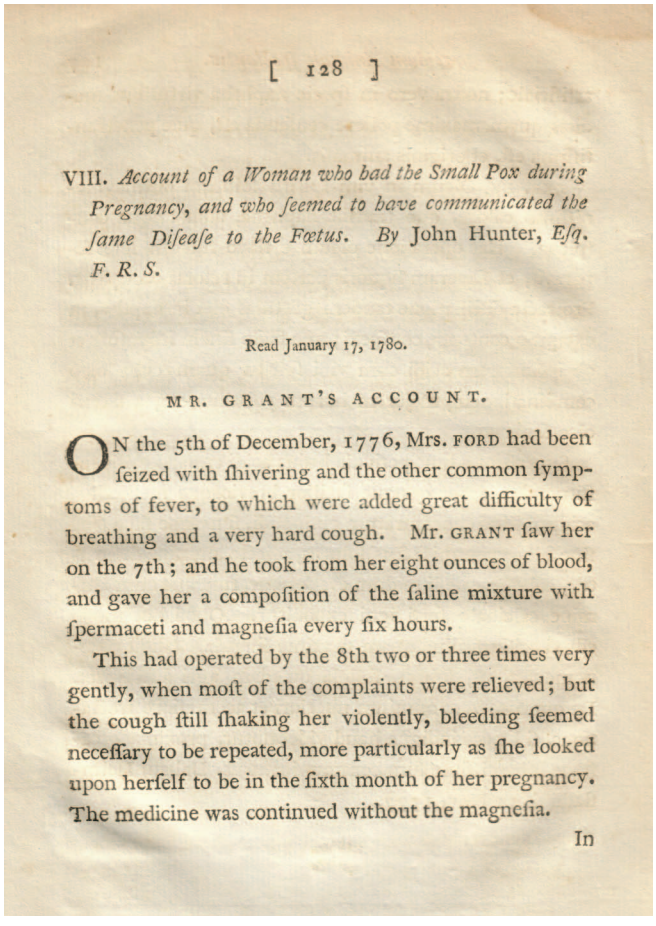
Smallpox and Pregnancy

Disease Course in Pregnancy.—In contrast to the few reported cases of mpox and cowpox in pregnant individuals, there have been hundreds of cases of smallpox disease in pregnancy, reported in the literature. It was recognized beginning in the early 1700s that a pregnant person infected with smallpox could transmit the infection to their unborn fetus and that smallpox in pregnancy could lead to preterm birth as well as miscarriage, stillbirth, or neonatal death. The Table summarizes publications from 18th-century Great Britain, illustrating examples of the state of the knowledge of smallpox in pregnancy, including reports from such famed physicians as William Smellie and John Hunter (Figure 1). The historical significance of smallpox in causing stillbirth is debated. Woods[20] has argued that smallpox infection during pregnancy was a significant cause of stillbirth in Great Britain during the 18th and 19th centuries, based on case reports and informal communications. In contrast, Schneider et al[21] analyzed parish-level data from the Swedish Tabellverket data set from 1780 to 1839. They found little evidence that smallpox had a significant role in causing stillbirths, primarily because most individuals had smallpox as children and were not susceptible to becoming infected during pregnancy.

A retrospective analysis summarized reports of the impact of smallpox on pregnancy outcomes across 19 outbreaks occurring during the 19th and 20th centuries.[22] Estimates of smallpox CFRs in pregnancy were highly variable, with the highest estimate of 81.5% in 1830 before widespread vaccination and the lowest estimate of 4.3% from Australia in 1913.[23,24] The overall crude CFR of smallpox in pregnancy was 34.3% (95% CI, 31.4%–37.1%), but this estimate is lowered by the inclusion of cases with variola minor and vaccinated individuals that had very low fatality rates.[22] Smallpox CFRs tended to be highest in the third trimester with a mean CFR of 40.5% (95% CI, 26.8%–54.2%).[22] In one of the largest case series of smallpox in pregnancy (n = 377), the CFR was double among unvaccinated pregnant women compared to nonpregnant adults (61.1% in pregnant women, 34.7% in nonpregnant women, and 30.2% in men).[25] Pregnant women were particularly vulnerable to the hemorrhagic-type of smallpox; one large case series estimated that there was a 7-fold and 3-fold higher risk of this disease form in pregnancy compared to men and nonpregnant women, respectively.[25] The hemorrhagic form of the disease was also uniformly fatal in pregnant women in several reports (57 deaths in 57 cases; 100%).[22] Overall, the CFR for smallpox in pregnancy was extremely high, especially for hemorrhagic disease and among unvaccinated individuals.

Reported Cases of Smallpox in Pregnancy From 18th-Century Great Britain		
Source, y	**Title**	**Summary of Findings**
Mortimer,[125] 1749	The case of a lady, who was delivered of a child, which had the smallpox appeared in a day or two after its birth	A baby delivered with smallpox after mother had contact with an infected person. The baby died of the infection a few days after delivery. The "mother took no infection"
Derham,[126] 1713	The case of a woman big with child, who recovered of the smallpox, and was afterwards delivered of a dead child full of the pustules of the distemper	An intrauterine fetal demise occurring 5 to 6 days before delivery. The stillborn fetus was "very full of the smallpox." The mother survived the infection
Stone,[127] 1737	Observation XXIX. The delivery of a woman being seized with the small pox, and brought in labour before her time	Preterm birth of a stillborn to a febrile mother, who dies from smallpox after delivery
Watson,[128] 1749	IX. Some accounts of the foetus in utero being differently affected by the smallpox	Describes 3 cases, in which 2 had smallpox infection of the fetus when the mother was previously infected
Smellie,[129] 1754	Case 83. Abortion at four months during small pox, death	A miscarriage at 4 months' gestation without marks on the fetus, mother died of severe hemorrhage. Two other cases of smallpox-related stillbirth
Wright,[130] 1781	XXIII. Account of a child who had the small-pox in the womb	In 1768 a pregnant Jamaican slave had smallpox and delivered a baby with signs of the disease. The baby died 3 days after delivery
Hunter,[131] 1780 (see Figure 1)	Account of a woman who had the small pox during pregnancy, and who seemed to have communicated the same disease to the foetus	A pregnant woman comes to London, develops smallpox, and has a stillborn fetus at 7 months' gestation with external signs of the disease

Data derived from [20]Woods R. *Death Before Birth: Fetal Health and Mortality in Historical Perspective*. Oxford University Press; 2009.



[128]

VIII. *Account of a Woman who had the Small Pox during Pregnancy, and who ſeemed to have communicated the ſame Diſeaſe to the Fœtus.* By John Hunter, *Eſq. F. R. S.*

Read January 17, 1780.

MR. GRANT'S ACCOUNT.

ON the 5th of December, 1776, Mrs. FORD had been ſeized with ſhivering and the other common ſymptoms of fever, to which were added great difficulty of breathing and a very hard cough. Mr. GRANT ſaw her on the 7th; and he took from her eight ounces of blood, and gave her a compoſition of the ſaline mixture with ſpermaceti and magneſia every ſix hours.

This had operated by the 8th two or three times very gently, when moſt of the complaints were relieved; but the cough ſtill ſhaking her violently, bleeding ſeemed neceſſary to be repeated, more particularly as ſhe looked upon herſelf to be in the ſixth month of her pregnancy. The medicine was continued without the magneſia.

In

Figure 1. *An article by famed British surgeon Dr John Hunter describes a smallpox case in a pregnant woman. Published in 1780 in the* Philosophical Transactions,[131] *the woman "seemed to have communicated the same disease to the foetus." From the collection of Dr Schwartz.*

Hemorrhagic Type of Smallpox in Pregnancy.—Several reports noted the propensity of pregnant individuals to the hemorrhagic type of smallpox in which bleeding in the skin and from multiple orifices was common.[22,25] Severe headache and backache were prominent features of the hemorrhagic form of smallpox, likely due to internal bleeding. This clinical picture appears similar to disseminated intravascular coagulation (DIC), which represents a systemic activation of coagulation resulting in microvascular thrombi and ultimate depletion of the body's clotting factors and uncontrolled bleeding.[25] Some studies indicated thrombocytopenia and a prolonged clotting and bleeding time in patients with early hemorrhagic smallpox, similar to what might be expected with DIC.[26] Pregnancy is a period of greater susceptibility to DIC, typically secondary to another cause such as placental abruption, postpartum hemorrhage, preeclampsia, retained stillbirth, acute fatty liver of pregnancy, or amniotic fluid embolism.[27,28]

If the hemorrhagic form of smallpox in pregnancy was due to DIC, it could be asked what triggered DIC. One possibility is that it might have been due to the retained stillbirth. In cases of hemorrhagic smallpox, fetal loss or preterm birth occurred in all reported cases.[22,29] Regardless of the clinical type of smallpox, fetal loss was extremely common. A retrospective analysis of 15 case series found that the overall crude proportion of "miscarriage" and preterm birth was 39.9% (95% CI, 36.5%–43.2%) for variola major and minor.[22] In the largest case series of pregnant individuals with smallpox (both types), nearly three-quarters of pregnancies ended in spontaneous abortion or stillbirth when the infection developed before 25 weeks of gestation.[29] The rate of stillbirth or preterm birth was approximately 60% when smallpox was acquired between 25 and 36 weeks of gestation, one of the highest among any viral infections during pregnancy.

VARV is not the only poxvirus that can result in hemorrhage and a "DIC-like" clinical picture. Consumptive coagulopathy is a rare feature of primary and secondary varicella-zoster virus infections in children and nonpregnant

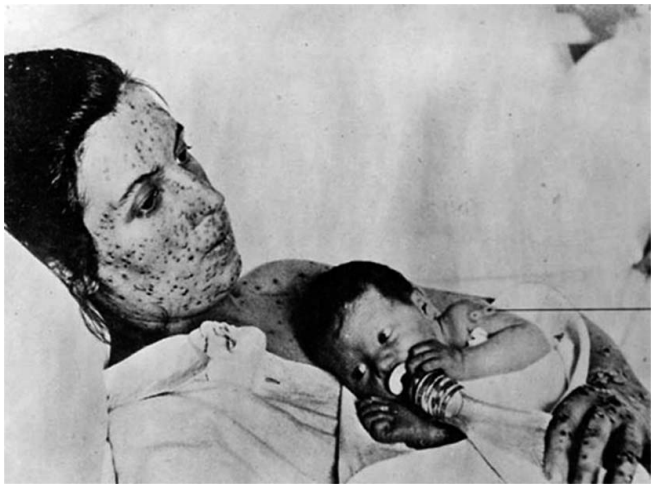


Figure 2. *A mother infected with smallpox, holding her vaccinated baby during the 1924 outbreak in Windsor, Canada. Reproduced from J. J. Heagerty.* Small Pox and Vaccination: A Popular Treatise. *Department of Health, Ottawa, Canada; 1924.*

adults (chickenpox and zoster, respectively).[30,31] Further, a marmoset nonhuman primate model of MPV infection was found to produce high viral loads, a hemorrhagic rash, and a decrease in platelets; this model was uniformly lethal and similar to the "early-type" of hemorrhagic smallpox in which death occurred within the first week of infection.[32] These findings indicate that a hemorrhagic clinical picture is possible with smallpox and other poxviruses, including MPV. Therefore, clinical surveillance for DIC seems appropriate when pregnant individuals develop an infection with MPV.

Maternal-Fetal or Perinatal VARV Transmission.—Evaluating published literature on the topic of obstetric outcomes from smallpox is challenging. The clinical terminology and diagnostic criteria had changed from that used during the early- and mid-20th and late 19th centuries when these studies were published (Figure 2). The extent to which congenital smallpox occurred in prior case series can also be problematic, as diagnosing the fetus or examining the placental histopathology was not a priority, or in many cases even a possibility, in the setting of the high fatality rates in pregnancy. However, in a case series of 34 cases of smallpox in pregnancy with mild disease (variola minor), 3 infants had an exanthem at birth and were diagnosed with congenital smallpox; one-half of the remaining infants developed an exanthem within 2 weeks of birth and were suspected of having been infected in utero or perinatally.[33] In a case series from Philadelphia, 4 infants had signs of smallpox infection and variola scars at the time of live birth, of whom 3 died within the first 2 weeks of life.[22] In addition, 3 aborted fetuses were also documented to have had signs of congenital smallpox. In an Australian case series, there were 2 cases of congenital smallpox in twins. One set of twins showed lesions at the time of birth and was found to be stillborn.[23] In the other set of twins, one was delivered stillborn with no evidence of lesions, while the live birth twin had lesions and ultimately died several days later. In a large case series from Madras, India, there were 10 neonates with congenital smallpox, with a CFR of 100%.[29] However, the incidence of congenital smallpox could be much higher since many infants died soon after birth, possibly before any signs of smallpox infection were present.

Placental and Fetal Pathology.—Very few pathology descriptions of VARV infection of the placenta and fetus were reported when compared with the large number of cases that occurred. Unfortunately, these reports present challenges in contemporary interpretation because the terminology and diagnostic criteria have substantially changed, as in clinical reports of smallpox occurring in pregnancy.

In 1963 Garcia[34] described 2 macerated stillbirths delivered to mothers having the alastrim type of smallpox. In the first case, a mother developed an infection during the fifth month of gestation and delivered a female fetus. The placenta was described as follows:

> The cotyledons were pink, with many minute yellowish areas irregularly spread over the maternal and fetal surfaces, conferring a minute granular aspect; the cut surface revealed an identical aspect; the membranes were thick and dark… Numerous granulomatous lesions, tuberculoid in type, were noted in the villi or in the conjunctive strands. These granulomas had central extensive necrosis, very like ceseastion. They were sharply circumscribed with wavy limits, surrounded by epithelioid cells, giant cells, histiocytes, and round cells… In the decidua the fibrinoid deposit was abundant, and the cell degeneration was remarkable. In these cells cytoplasmic acidophilic inclusion bodies of various sizes (Guarnieri bodies) limited by clear space, were found. Intranuclear inclusions were found equally; they were usually single, oval, and homogenous masses, surrounded by a halo, separating them from the rest of the nucleus, which was sometimes reduced just to its nuclear membrane with a few chromatin dots.

The second case concerns a mother who developed alastrim in her fourth month of pregnancy, followed 20 days later by spontaneous abortion.[34] The fetus was macerated and demonstrated small, whitish, round (5 mm) dorsal cutaneous lesions that were irregularly spread. Microscopic examination of fetal organs, "in spite of the degree of maceration of the viscera, revealed minute and not well-defined areas of necrosis in the lungs, thymus, kidneys, spleen, adrenals and liver." The placenta weighed 90 g and "the maternal side appeared with a mottled aspect, with minute intermingled pink and yellow areas. After fixation, innumerable small yellow dots of creamy consistency were seen in the parenchyma." Microscopic examination of the placenta demonstrated that "The intervillous space was occupied by a heavy exudate, consisting of amorphous material and leukocytes (polymorphonuclear cells and cell debris)… An increase of round cells and little areas of necrosis appeared in the stroma… In the decidual cells, there was a cytoplasmic inclusion, such as a paranuclear homogenous corpuscle of irregular size…"

It is difficult to conclude from these and other historical descriptions of the effects of VARV infection on the placenta, partly because few placentas were pathologically examined, and those were mostly from cases of spontaneous abortion and stillbirth that was often macerated.

EXPERIMENTAL ORTHOPOXVIRUS INFECTIONS AND PLACENTAL PATHOLOGY

Scant information is available on the effects of orthopoxvirus infections in humans and the placenta. Unfortunately, the published experimental animal studies conducted in

pregnant mammals have provided little information on the interaction between orthopoxviruses and placental cell types. Although the human placenta is structurally and physiologically unique, experimental animal studies of placental pathology have the advantage of good tissue preservation and detailed information on route, timing, and dosage of inoculum as well as clinical-pathologic correlation; they also have the disadvantage that most mammalian placentas have differences in placental structure and perfusion from that of humans.

Studies of mid- to late-gestation experimental vaccinia inoculation in pregnant mice (*Mus musculus*) have reported total fetal mortality.[35] Low-dose administration of vaccinia virus (VACV) to mid-gestation pregnant mice via either the intravenous or intraperitoneal routes resulted in rapid placental infection but delayed intrauterine transfer to the fetus, with only 19% of fetuses infected by 4 days post inoculation. In contrast, high-dose intravenous inoculation of the virus resulted in a substantially greater viral load in the placenta and rapid vertical infection of vaccinia to the fetus. Molecular analysis of the placentas 4 days following intravenous administration of VACV showed that viral nucleic acid transcripts were present exclusively in placental cells that were adjacent to, or lining, large maternal blood vessels (maternal lacunae) within the trophospongium layer (a thick multicellular layer of fetal trophoblasts separating the decidua from the labyrinth). By 7 days post inoculation, VACV had spread from the maternal blood spaces in the trophospongiosum to other parts of the murine placenta, including labyrinthine cells of the fetal side adjacent to the chorionic plate and the cells lining the blood vessels in the uterine decidua and trophospongium.

In the baboon (*Papio anubis*) experimental model, Kalter et al[36] divided pregnant animals into 3 groups and inoculated them intravenously with VACV during the first, second, or third trimester of pregnancy. The placenta and fetuses were removed and examined at 2, 4, and 7 days following inoculation. The virus was isolated from the skin, muscle, spleen, liver, or amniotic membrane in 3 of 8 fetuses. VACV was not isolated from any of the placentas, and microscopic placental examination did not demonstrate any lesions that could be the result of viral infection.

MPOX

Mpox in Africa

Mpox was first recognized in 1958 after 2 pox-like skin eruption outbreaks in captive rhesus macaques (*Macaca cynomolgus*) that had arrived in Copenhagen after being shipped from Singapore.[37] Inoculum from the skin lesions produced pock lesions after being inoculated on chorioallantoic membranes of chick embryos, cytopathic effects in mammalian cell cultures, and pathologic tissue lesions in experimental mice and rabbit inoculation. Ultrastructural studies revealed the virus resembled poxviruses, and as it antigenically resembled members of the vaccinia-variola subgroup of poxviruses, it was termed *monkeypox*.[38] During the following decade, there were 8 more outbreaks among several institutions that had imported nonhuman primates from India, the Philippines, and Malaysia.[38–40]

The first human infection with MPV was identified in 1970 when a 9-month-old child was admitted to the Basankusu Hospital in Equatorial Province, Democratic Republic of Congo (DRC). He was initially suspected of having smallpox, as he was unvaccinated, but was found to be infected with MPV.[41] Additional cases of MPV were subsequently recognized from the DRC and other African countries, including Liberia, Sierra Leone, the Central African Republic, Nigeria, Cote d'Ivoire, South Sudan, Gabon, and the Republic of the Congo.[42–47] The DRC has had the greatest number of MPV infections—from 1981 to 1986, the WHO identified 338 confirmed cases and 33 deaths for a CFR of 9.8%. In the DRC, between 1991 and 1998, there were 511 cases reported,[48] with some estimates of greater than 2000 suspected cases of MPV infection occurring annually.[49] Between January and September 2020 alone, there were 4594 suspected MPV infections.[50] Since the initial reports of human MPV infections, the number of cases has increased at least 10-fold. In addition, whereas the disease had initially been an infection of young children, there has been an increase in the median age at presentation from 4 to 5 years of age in the 1970s to young adults up to 21 years of age from 2010 to 2019.[1,51] Mpox often occurs in regions associated with tropical rainforests but has been increasingly identified in urban areas.[42] In Africa, evidence of MPV had been found in a wide variety of mammals, including squirrels (*Funisciurus* spp and *Heliosciurus* spp), dormice (*Graphiurus* sp), and Gambian pouched rats (*Cricetomys gambianus*). Although rodents are suspected of being the natural host, it has not been confirmed.[42,52] Although MPV-specific antibodies have been identified in very few monkeys, they are probably similar to humans in being only occasional hosts of the MPV.

There are 2 genetic variants, termed *clades*, of MPV that occur in Africa: Clade I (termed the *Central African* or *Congo Basin clade*) and Clade II (termed the *West African clade*). These 2 clades are geographically distinctive and have important epidemiologic and clinical differences, with the Congo Basin clade having greater pathogenicity.[42] The West African clade was identified in isolates obtained during MPV outbreaks in Sierra Leone, Nigeria, Liberia, Ivory Coast, and the United States, where it was imported from Ghana; it has a CFR lower than 1%, and no human-to-human transmission has been reported. In contrast, MPV isolates of the Congo Basin clade originating from DRC, Republic of Congo, Sudan, Gabon, Cameroon, and Central African Republic have a CFR of up to 11%; multiple cases of human-to-human transmission have been reported along with a higher frequency of viremia.[48,53] To address issues of stigma and discrimination, the WHO convened a meeting of experts in August 2022 to propose a neutral naming system of the virus. In addition to renaming the disease mpox, these experts recommended dividing Clade II into 2 phylogenetically distinctive subtypes, termed *IIa* and *IIb*.[54] The marked genetic differences between Clades I and II are nearly twice as divergent as are the genetic differences between Clades IIa and IIb.[54] Genetic analysis indicates that the current global outbreak was caused by a divergent branch of Clade IIb MPV that has genetic linkage to the viruses that resulted in the 2017 and 2018 outbreaks in Nigeria, an endemic country, and cases that were exported from there to Israel, Singapore, and the United Kingdom in 2018 and 2019.[55] There are remarkable genetic similarities between VARV and MPV, with genomic analysis demonstrating a 96.3% identity in the central portion of the genomes encoding for structural proteins and essential enzymes, but with significant differences in the end regions encoding for host-range specificities and virulence.[56,57]

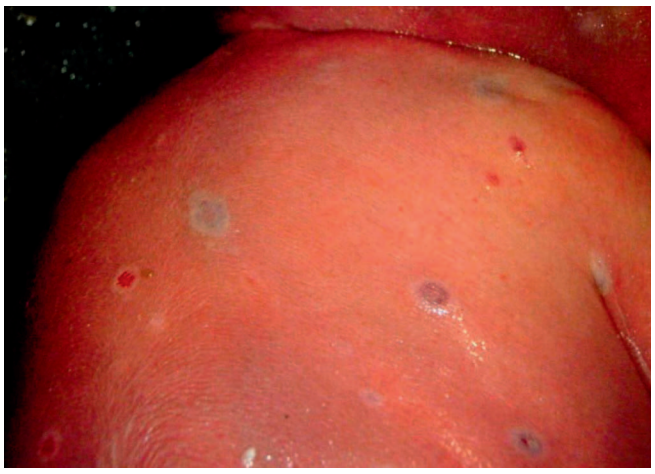


Figure 3. *Photograph of the right shoulder and back of a stillborn fetus with congenital mpox syndrome. The features of the mpox lesions are evident and were present diffusely on the skin of the scalp, face, abdomen, back, shoulders, chest, and trunk, as well as extremities, including the palms and soles of the hands and feet.*

Mpox in Pregnancy in Endemic African Countries

Before the 2022 outbreak, there was little attention paid to MPV infections in pregnancy despite the large numbers of infected children and adults in DRC and elsewhere in Africa. As a result, scant data existed regarding the spectrum of maternal clinical illness from MPV, its effects on the fetus and placenta, and its capability for vertical transmission.[58]

In 1988 Jezek and Fenner[59] described a probable case of perinatal MPV infection that had occurred in DRC. Although it was not confirmed by laboratory identification of the virus, the clinical circumstances and features led to a high probability that it represented a case of vertical MPV transmission. The pregnant individual developed clinical evidence of mpox at approximately 24 weeks' gestation and 6 weeks later delivered a premature infant with a generalized skin rash suggestive of mpox disease. The infant died from malnutrition 6 weeks after birth. No pathology studies were performed.

Most data available on mpox in pregnancy are derived from the Kole Human Monkeypox Infection Study initially conducted in the Sankuru Province of DRC from March 2007 to July 2011.[60–62] To study the natural history of mpox disease, Mbala et al[60] examined a cohort of 222 symptomatic patients (36% female, 64% male) who were seen at the General Hospital of Kole, in a remote town in a region of tropical rainforest where the population resides in small villages surrounded by traditional agricultural fields. The inhabitants of this region are mostly farmers and hunters who have close contact with a broad range of indigenous animal species.

Four women in this cohort developed polymerase chain reaction (PCR)–confirmed MPV infection during pregnancy.[60] Case 1 involved a mother who developed MPV infection at 6 weeks of gestation and had a miscarriage 24 days following the onset of disease, manifested by the development of fever. She had moderate mpox disease characterized by 76 skin lesions. Case 2 involved a woman who became febrile at 6 to 7 weeks of gestation and developed severe MPV infection with 1335 skin lesions. She had a miscarriage 14 days after onset of fever. Case 3 involved a woman who was the only mother with MPV infection whose fetus survived. She developed a fever at 14 weeks' gestation, had mild clinical mpox disease with 16 skin lesions, and delivered a liveborn full-term uninfected newborn. Case 4 is described in the next section.

Yinka-Ogunleye and colleagues[63] described an MPV infection that resulted in a stillborn fetus at 26 weeks' gestation, following mpox clinical disease of the mother during a 2017–2018 Nigerian outbreak. No description of the fetus or confirmatory testing was available.

Another case of mpox in pregnancy occurring in Nigeria during the same time frame was described by Ogoina et al.[64] This pregnant woman had MPV infection and a spontaneous abortion at 16 weeks' gestation accompanied by spontaneous rupture of membranes. No additional information was available.

All 7 mpox infections among pregnant women in Africa occurred in just 2 countries where the disease is endemic—DRC and Nigeria. Unlike some other viral diseases occurring during pregnancy in these regions, mpox has not been responsible for maternal deaths. All 7 mothers had symptomatic mpox infection with characteristic skin lesions. Two of the 7 pregnancies resulted in liveborn neonates, with one surviving and the other dying 6 weeks after birth. Both pregnancies resulted in preterm delivery. The remaining 5 pregnancies resulted in fetal deaths, with 3 miscarriages before 20 weeks' gestation and 2 cases of intrauterine fetal demise occurring at 21 and 26 weeks' gestation.[65]

Intrauterine Mpox Transmission With Placental Infection and Stillbirth—The Congenital Mpox Syndrome

Among the 4 individuals with mpox during pregnancy in the DRC, as summarized by Mbala et al,[60] case 4 described a pregnant woman who was positive for malaria. She had an onset of fever at 18 weeks' gestation and developed a moderate MPV infection with 113 skin lesions. MPV viremia was diagnosed, which quickly rose from 10^2 to 10^6 copies/mL upon cessation of fetal movement. Twenty-one days after the onset of fever, she delivered a stillborn fetus at 21 weeks' gestation.[60,61] This case is of significance as it is the only MPV infection occurring during pregnancy with extensive laboratory, molecular microbiology, and pathology evaluation that resulted in an intrauterine fetal demise. Specimens taken at the time of membrane rupture and transcutaneous amniocentesis were blood tinged, and PCR identified MPV at the level of 2.6×10^7 genome copies/mL. Fetal blood obtained from the umbilical vein was positive for MPV by PCR at 2.5×10^7 genome copies/mL. An autopsy of the stillborn fetus was performed. Fetal tissue contained 1.7×10^7 MPV genome copies/mL, and sterile peritoneal fluid was positive for MPV at a level of 1.6×10^3 genome copies/mL by PCR. External examination of the fetus revealed numerous diffuse cutaneous maculopapular lesions, consistent with those of mpox, which diffusely involved the skin of the abdomen, back, shoulders, chest, head, and the extremities including the palms of the hands and soles of the feet (Figure 3). Hydrops fetalis was present together with prominent hepatomegaly and peritoneal effusions. These findings represent a congenital mpox syndrome (Figure 4). PCR of the placenta was positive for MPV at a level of 2.4×10^7 copies/mL. Gross placental examination demonstrated an unusual pattern of punctate basal hemorrhages spread over the maternal surface of the placenta. Our evaluation of immunohistochemistry, using an antibody to VACV with broad orthopoxvirus reactivity, demonstrated strong positivity within the cytoplasm of villous stromal cells

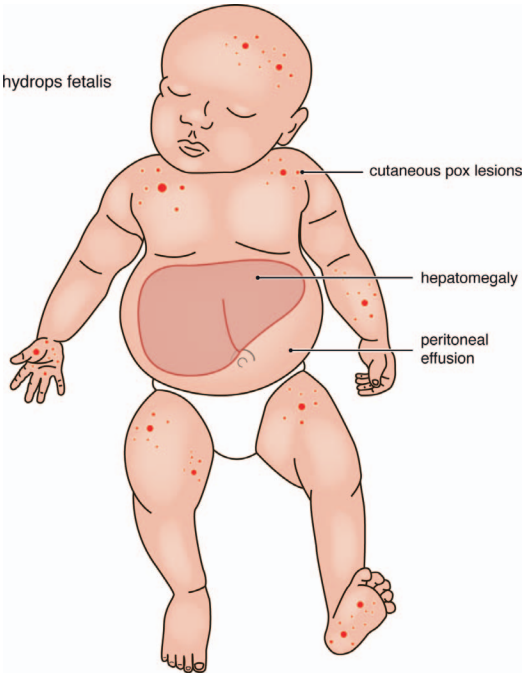


Figure 4. *Graphic illustration of the features in the congenital mpox syndrome.*

that were consistent with Hofbauer cells.[60–62] These cells also appeared to have increased in number—termed *Hofbauer cell hyperplasia*.[61,62] This case demonstrates that MPV can be transmitted through the placenta from an infected mother to the fetus (Figure 5), adding this virus to the list of TORCH agents (*Toxoplasma gondii*, other, rubella virus, cytomegalovirus, herpes simplex virus).

Mpox in Pregnancy During the 2022 Global Outbreak

The 2022 mpox outbreak was first recognized in an individual in Great Britain who had travelled to Nigeria, where he developed a rash on April 29, 2022, before flying to London on May 4. Immediately hospitalized upon his return, MPV infection was confirmed on May 6. Contact tracing was initiated, and by May 20, twenty additional infected individuals were identified with no history of foreign travel. The number of MPV cases in Great Britain rapidly multiplied throughout May, and by June 10, there were 314 infected patients, of whom 311 were men.[66,67] The infection spread to other European countries and thereafter to the United States, Canada, South America, the Middle East, Asia, and Oceania. Most cases occurred in men (99%), with 98% occurring in men who have sex with men, among whom major risk factors included having multiple sex partners and being HIV-positive.[68] Additional epidemiologic and clinical factors identified during the outbreak differed from historical features of infection in endemic countries, including a greater frequency of genital involvement and decreased likelihood of prodromal symptoms.[8,69] As of February 16, 2023, mpox had occurred in 110 countries or territories, infected 85 860 persons, and caused 93 deaths.[70]

The 2022 mpox outbreak occurred almost exclusively in men; however, women, pregnant individuals, and neonates have also become infected.[71] Fifty-six pregnant persons have been identified as of February 14, 2023, as having had mpox infection during the 2022 global outbreak.[72] Among these, the average age was 28 years. The infection occurred during

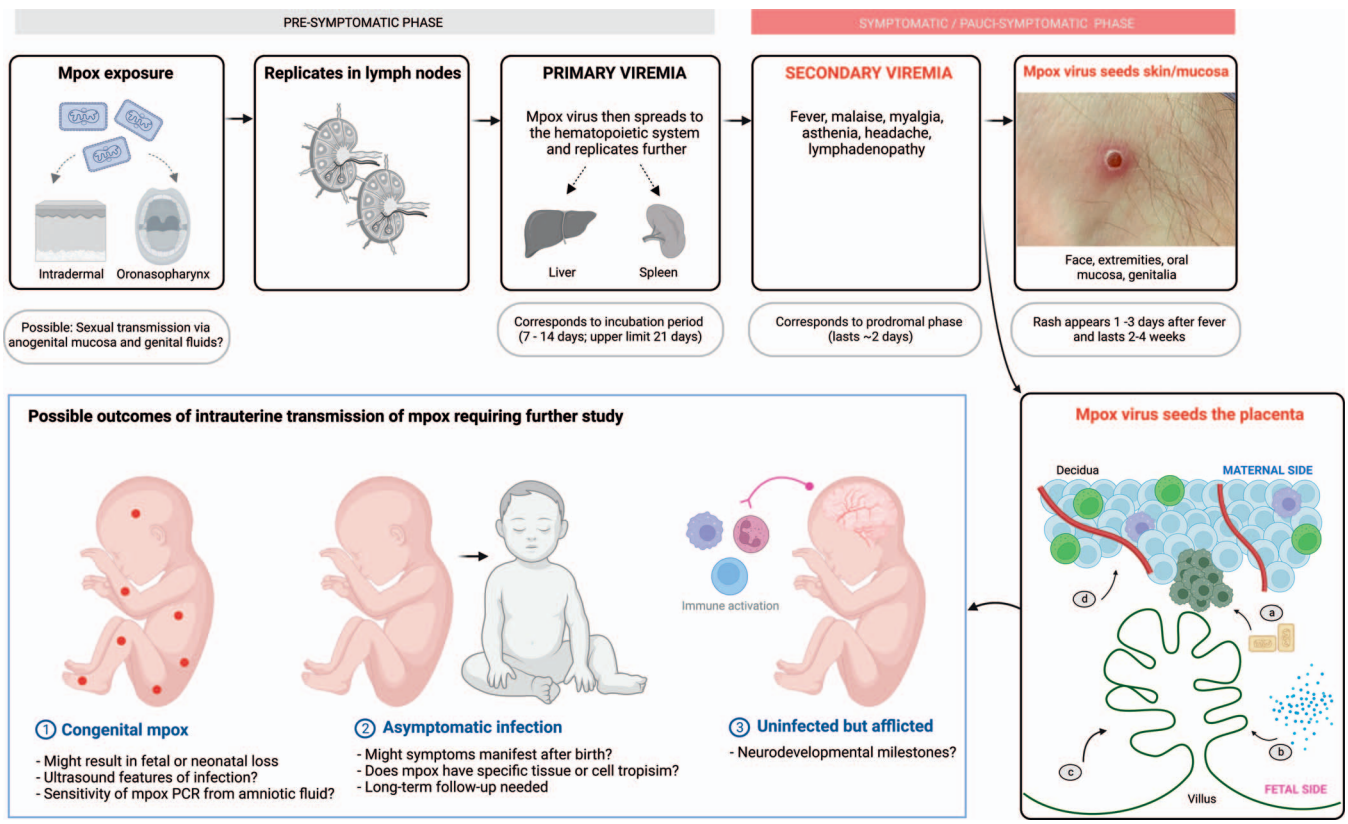


Figure 5. *Pathogenesis of mpox (monkeypox) infection during pregnancy. Abbreviation: PCR, polymerase chain reaction.*

the first trimester in 4 cases, second trimester in 12 cases, and third trimester in 10 cases, with no data available for 30 individuals. In addition, mpox was identified in an individual who was 6 weeks or fewer postpartum. Thirteen of these individuals were hospitalized.

In the United States, 21 persons have been identified with mpox during pregnancy with 2 persons infected within 3 weeks of pregnancy during the period May 11 to November 7, 2022. These 23 cases represent 3% of 769 cases of MPV infection occurring in cisgender women.[73] The first case was identified in the United States on July 23, and although details are unavailable, the fetus was reported to be uninfected.[74,75]

Brazilian health authorities reported 9 cases of MPV infection among pregnant people by August 26, 2022.[76] These included 4 in São Paulo, 3 in Rio de Janeiro, and 1 each in Minas Gerais and Ceará.[77] Eight of the 9 cases were confirmed by PCR testing for MPV; the pregnant individual from Ceará tested negative. A local Sao Paolo newspaper reported on August 5 that one of the infected mothers had passed the transmission phase, and that the mother and baby were in stable condition, but did not address potential vertical transmission.[76,78] In Minas Gerais, a pregnant person with MPV infection presented to the hospital with skin lesions; she delivered a healthy baby on August 14. Following isolation from her baby after delivery, they were discharged on August 17 with no evidence of vertical transmission.[76,79] As of January 16, 2023, a total of 22 pregnant persons in Brazil have had either confirmed or suspected mpox, with 2 requiring hospitalization and treatment.[80] In none of the cases from Brazil, the United States, or elsewhere during the 2022 mpox outbreak was intrauterine or placental infection identified.

In October 2022, the case of a neonate with mpox was reported by Ramnarayan et al[81] from Great Britain. Following an uneventful pregnancy and delivery, a 9-day-old neonate developed a characteristic vesicular rash of mpox accompanied by axillary lymphadenopathy. PCR testing from multiple sites revealed the neonate was infected with MPV, and adenovirus was identified from respiratory secretions. The rash began as vesicles that involved the palms and soles; it then spread to the face and trunk before becoming pustular. The clinical condition of the newborn became severe, requiring intensive care with 2 weeks of ventilation and administration of enteral tecovirimat (an antiviral medication with activity against orthopoxviruses) and intravenous cidofovir (an antiviral medication generally used for cytomegalovirus with activity against MPV). Eventually, the neonate recovered. Epidemiologic evidence strongly suggested that this was a case of postnatal vertical infection originating from parental contact following birth. Nine days before delivery, the father developed a fever and diffuse rash, which resolved before the baby's birth. Four days after delivery, the mother developed a rash similar to the father's, which was confirmed to be MPV infection by PCR.

Pathogenesis of Vertical MPV Infection, a TORCH Agent

MPV can infect the host after exposure via the nasopharynx, oropharynx, or intradermal routes. Following viral replication at the inoculation site, the infection spreads to regional lymph nodes. Following a period of initial viremia, the virus can spread to other body organs where replication and secondary viremia occur, typically associated with fever. The virus ultimately infects the skin, causing the characteristic "pock" rash.

The demonstration of a stillbirth resulting from placental and fetal infection with MPV adds this virus to the list of "Other" among the TORCH agents.[60–62] TORCH is an acronym that was introduced in 1971 for microbial agents that can infect the placenta and fetus, resulting in congenital infection.[82–84] This acronym was proposed by Nahmias and colleagues[84] in Atlanta, Georgia, to refer to the commonly identified causes of vertically transmitted infections that were recognized at that time. The list has since been greatly expanded and includes other viruses that have caused recent outbreaks and epidemics, including the Ebola virus,[85] Zika virus,[86–89] and most recently, SARS-CoV-2.[90–93]

There are several potential routes by which TORCH viruses can cause intrauterine infection during pregnancy.[94] To access the intraamniotic compartment, viruses must overcome innate immune responses, the first line of defense preventing vertical transmission, which are organized by maternal and fetal cells at the decidual-placental interface. Viruses must also penetrate the placenta, a complex chimeric organ that is the primary barrier preventing the passage of infectious agents from maternal tissues to the fetus. These routes include penetration through damage or breaks in the syncytiotrophoblast cell layer (which separates the maternal circulation in the intervillous space from the fetal chorionic circulation); infection of the syncytiotrophoblast cells; infection of extravillous trophoblast and other cells (possibly through the maternal microvasculature and endothelial cells); trafficking through infected maternal immune cells; paracellular or transcellular transport; and ascending infection from the maternal cervicovaginal canal.

In mpox infection, Dashraath et al[71] have proposed 4 specific pathways by which the virus can result in intrauterine transmission. Among these mechanisms is the maternal-fetal transmission of MPV following an episode of maternal viremia, in which the virus reaches the placenta through the uterine arterial blood supply. This mechanism of hematogenous transmission was likely responsible for the transplacental infection resulting in an MPV-infected stillborn fetus that occurred in the DRC (Figure 5). In this case there was confirmed maternal viremia and positivity in stromal cells—termed *Hofbauer cells*—within the chorionic villi of the placenta, identified by immunohistochemistry.[61,62] A similar mechanism in which placental infection occurs as a result of maternal viremia has recently been proposed for SARS-CoV-2 by Schwartz et al.[95] Importantly, the 2022 mpox outbreak has provided data suggesting viral clade differences are significant factors in obstetric outcome. Clade I mpox infections that occurred in DRC resulted in perinatal death in 75% of cases when the mother was infected[60]; in contrast, infection with the mpox Clade IIb that is causing the 2022 global outbreak has not been reported to result in miscarriage, stillbirth, or intrauterine infection.

Many questions remain to be answered: When exactly is MPV transmitted from the pregnant person to the fetus? Is there a relationship between fetal infection, the timing of maternal MPV infection, and gestational age? Are maternal conditions or other factors putting the fetus at high risk of vertically acquiring the MPV? What is the placental pathology of MPV? Among pregnant people with MPV infection, are fetuses at a higher risk of acquiring the MPV during labor than at other stages of pregnancy? Is breastfeeding a risk for postnatal transmission of MPV?

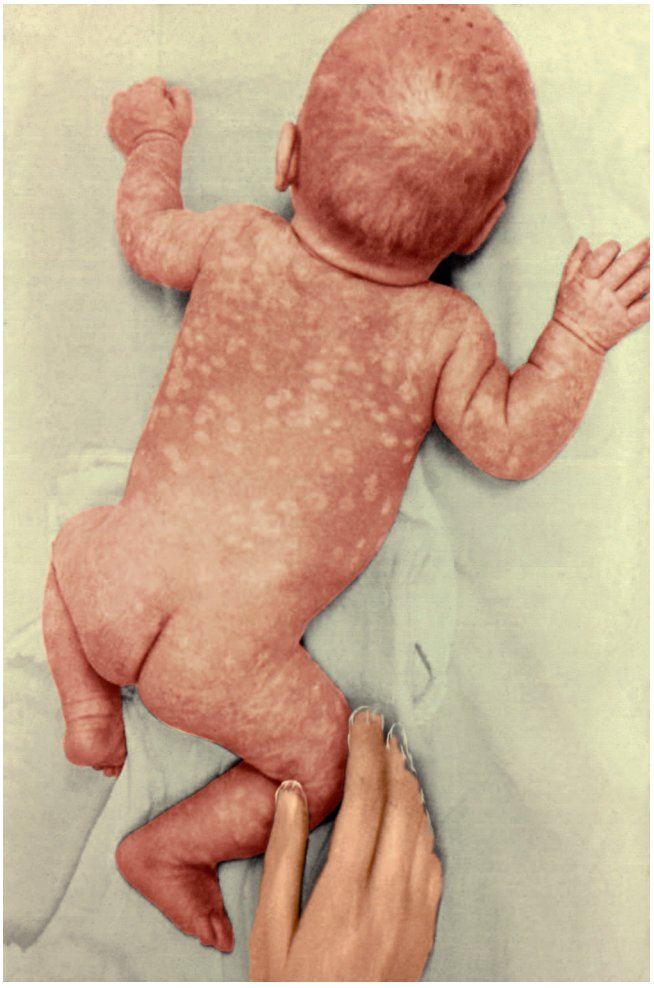


Figure 6. *This 1969 image shows a neonate with extensive scarring after contracting intrauterine vaccinia virus infection. Fetal vaccinia can occur after primary smallpox vaccination of a pregnant woman in the second or third trimester from hematogenous spread of the virus to the amniotic fluid, or directly to the fetus. Photograph courtesy of the Centers for Disease Control and Prevention.*

What is the role of prior immunity against MPV during pregnancy in previously exposed people? Does previous maternal vaccination for smallpox affect vertical transmission? Is intrauterine fetal infection only transient, as reported for the Zika virus[96]? What is the rate of vertical infection during each trimester, and in the case of fetal infection, what is the rate of symptomatic fetuses? It also remains to be determined if pregnancy impacts the clinical progression of MPV infection in the pregnant individual.[89,97,98]

OTHER ORTHOPOXVIRUSES: HUMAN DISEASE AND PREGNANCY

Cowpox Virus

Cowpox virus (CPXV) infects dairy cows, where it typically affects the udders. It can be transmitted to humans, mainly occurring in the hands of dairy workers coming into direct physical contact with the infected udders during milking. CPXV entered medical history in 1796 when Dr Edward Jenner noticed that English milkmaids who had been infected with cowpox were subsequently immune to smallpox, leading to the development of the smallpox vaccine.[99]

In 2021, a pregnant woman at 11 weeks' gestation presented to a hospital in France with lesions on her hands, fingers, and chin accompanied by fever and adenopathy.[100] The following week, PCR testing was positive for a non-smallpox orthopoxvirus, and cowpox was diagnosed at the National Reference Laboratory from all samples except for plasma, which was negative. One week after her initial presentation, the fetus died. CPXV DNA and infectious virus were identified in the placenta and fetus; 2 weeks later, CPXV was isolated in a vaginal specimen.

Vaccinia Virus

The current smallpox vaccines contain VACV, which is distinct from cowpox and smallpox viruses. Fetal vaccinia infections are believed to result from maternal viremia and are associated with skin lesions and visceral organ involvement.[101] Because of this, the recommendation has been that smallpox vaccination should not be administered within 4 weeks before or during pregnancy in the absence of circulating smallpox.[101]

Transmission of the VACV to persons having close contact with an infected individual has been demonstrated, including for children and spouses.[102] Fetal infection has been reported in cases where pregnant people were exposed to VACV during vaccinations to prevent smallpox infection (Figure 6). In one case, a woman developed VACV blepharoconjunctivitis in her tenth week of pregnancy.[103] Her infection was believed to originate from exposure to her 15-month-old son, who had received a vaccination. She developed generalized vaccinia, which resulted in a spontaneous abortion. MacArthur[104] studied vaccinia administration among pregnant mothers in Glasgow, finding that it was associated with a higher incidence of fetal death, particularly among women vaccinated during the second and third months of pregnancy. A recent meta-analysis examining pregnant individuals receiving the smallpox vaccine disclosed 21 cases of fetal vaccinia, of whom only 3 neonates survived, with a CFR of 86%.[105]

However, maternal vaccinia infection does not always lead to fetal involvement. Sommacal and Lerner[106] described the case of a pregnant woman at term who developed disseminated vaccinia infection following exposure to her recently vaccinated children and delivered a healthy uninfected baby.

Although the current third-generation smallpox vaccines are composed of live attenuated VACV and are thus infectious, the overall risk for administering the smallpox vaccine to pregnant people is low.[105] Among recent studies of pregnant individuals who have received the smallpox vaccine, either without knowledge of their pregnancy status or because of certain professional or personal risk factors, there have been no statistically recognized adverse effects.[107] Ryan et al[108] reported no association between receiving the vaccine in the first trimester of pregnancy and prematurity, congenital infection, or other adverse outcomes among 7735 infants delivered to active-duty military women vaccinated against smallpox and 672 infants born to mothers in the military.

DISCUSSION

Three genera of Poxviridae have been identified as causing human infections—orthopoxviruses, yatapoxvirus,

and parapoxviruses. Except for molluscum contagiosum and VARV, human poxvirus infections are zoonotic, resulting in sporadic human infection predominantly affecting the skin.[109] Tanapox,[110,111] Orf virus,[112] pseudocowpox virus,[113] CPXV,[114] buffalopox virus,[115] camelpox virus,[116] and the vaccinia-like Araçatuba virus,[117] and Cantagalo virus[118,119] are potentially emerging poxvirus infections in humans associated with low levels of morbidity and, thus far, no cases reported during pregnancy.

VARV was the most prominent member of the Poxviridae family to cause human disease, with epidemics and pandemics of smallpox extending back to ancient times. Following the last naturally acquired case of smallpox that occurred in southern Somalia in October 1977,[120,121] other poxviruses have continued to cause infections, typically due to introduction into human populations from a zoonotic source. However, the only naturally occurring poxvirus infection that currently presents a real danger during pregnancy is mpox.[122]

Before the 2022 outbreak, there were 7 published cases of mpox in pregnant individuals.[59,60–64] Based on its widespread demographic distribution as an endemic virus in rural Africa, it is probable that there were other cases of mpox during pregnancy that have not been reported. With the recognition that vertical MPV transmission can occur via antenatal transplacental infection[60–62] and postnatal environmental exposure,[81] there remains no doubt of the potential for MPV to affect the fetus and neonate. Like smallpox infection, mpox has a significant potential to cause maternal viremia and poor fetal outcomes, including spontaneous abortion, stillbirth, and maternal-fetal transmission with congenital infection, thereby the classification of MPV as a TORCH agent. The risk of fetal loss appears to be similar whether MPV infection is acquired during the first or second trimester.[65] In addition, MPV has been found to infect fetal-derived cells in the placenta,[62] as do other TORCH viruses, including SARS-CoV-2, Zika virus, Ebola virus, and cytomegalovirus. Unlike these viruses, MPV has not been well studied, and only a single fetus and placenta with congenital infection has been investigated.[60–62] It is unfortunate that until the 2022 mpox outbreak, this poxvirus infection remained neglected by most of the public health and medical communities. Despite MPV causing many thousands of cases and fatalities in endemic African countries since its recognition as a human pathogen in 1970, there are only scant data available on the natural history of the infection during pregnancy, the risk of vertical infection, the efficacy and safety of vaccination of pregnant individuals, and the effects on the placenta and fetus. The lack of attention and funding directed toward this emerging poxvirus infection by the public health and medical communities has resulted in lost years of potential research to understand better the prevention, surveillance, investigation, and clinical management of mpox.[123,124] The termination of routine smallpox vaccination among the general population in the United States in 1971 and elsewhere has led to persons in the reproductive age group now being susceptible to orthopoxvirus infections, including mpox.[121] The recognition of MPV as a TORCH agent emphasizes the immediate need for additional clinical and scientific studies of this virus in pregnancy and comprehensive maternal and fetal surveillance in pregnancies complicated by MPV infection.

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