



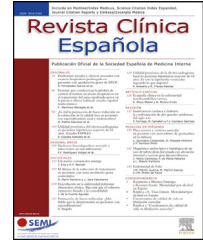
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REVIEW

Monkeypox and pregnancy: A neglected disease and its impact on perinatal health

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KEYWORDS

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Abstract Viral infections during pregnancy have been one of the leading causes associated with significant perinatal problems, such as congenital defects, fetal neurological syndromes, stillbirths, and adverse pregnancy outcomes. The monkeypox virus infection, caused by an Orthopoxvirus related to the human smallpox virus, was declared a global health emergency by the World Health Organization in July 2022 due to the large number of cases emerging outside the usual endemic area in Africa. There is little information on the impact of monkeypox virus infection during pregnancy, although the limited evidence available shows a high rate of fetal harm. This review addresses the problem of monkeypox virus infection in pregnant women and provides indications for its prevention, diagnosis, and treatment.

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PALABRAS CLAVE

Viruela del mono;
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Vacunación

La viruela del mono y el embarazo: una enfermedad olvidada y su impacto en la salud perinatal

Resumen Las infecciones virales durante el embarazo han sido una de las principales causas asociadas a problemas perinatales de gran importancia como lo son daños congénitos, síndromes neurológicos fetales, abortos y desenlaces adversos de la gestación. La infección por el virus de viruela del mono, causada por un Orthopoxvirus emparentado con el virus de la viruela humana, ha sido declarada por la Organización Mundial de la Salud en julio de 2022 una emergencia de salud global ante el gran número de casos surgidos fuera del área endémica habitual en África. Existe poca información sobre el impacto de la infección por el virus de la viruela del mono

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durante el embarazo, aunque las escasas evidencias disponibles muestran una alta tasa de daño fetal. En esta revisión se aborda el problema de la infección por el virus de la viruela del mono en mujeres embarazadas, proporcionando indicaciones para su prevención, su diagnóstico y su tratamiento.

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Introduction

Multiple cases of monkeypox have been reported in recent months in areas of the world where this disease is not endemic.¹ In July 2022, the World Health Organization (WHO) declared the outbreak of infections caused by the virus a global Public Health Emergency, with close to 16,836 cases across 74 countries (Fig. 1).²

Clinical evidence regarding monkeypox virus infection in pregnancy is limited, primarily due to the socio-economic situations and civil conflicts in many of the countries where this viral infection is endemic. Therefore, it is important to create and document new medical literature regarding possible vertical transmission and the effects on the health of the mother-baby pair.

In this regard, the following review focuses on the existing evidence of the effects of monkeypox infection during pregnancy, as well as clinical and prophylactic recommendations such as vaccination, and the hypothesis of a placenta effect via maternal infection that this emerging virus could disrupt positive outcomes during gestation.

Clinical and virological characteristics of the monkeypox virus

Monkeypox virus belongs to the *Orthopoxvirus* genus of the *Poxviridae* family. Structurally, these viruses are oval shaped and between 200 and 400 nm in length.³ These viruses have a complex capsid architecture, containing 100 different proteins and their genome, a double chain deoxyribonucleic acid (DNA), contains approximately between 133 and 229 genes. The genome replicates in the cytoplasm of the host cell.^{4,5}

Epidemiological studies state that the monkeypox virus was first identified in a group of macaques imported from Singapore in 1958. Zoonotic infection in humans was not identified until 1970 when the first case was reported in the Democratic Republic of the Congo.⁶

Epidemiological studies have identified the genetic diversity of the virus, suggesting the presence of 2 clades depending on their geographic distribution: the west African clade, associated with cases in other areas where the infection is not endemic and the case fatality rate is less than 1%, and the central African clade (Congo Basin), which is more virulent and has a case fatality rate of 10%.⁷

Since it was first detected, this pathogen has been endemic to eastern and central Africa, with thousands of

cases reported annually in this part of the world.⁸ Cases were imported from the African continent in 2003 with infections in the United States, United Kingdom, and Singapore.⁹ Currently, close to 16,000 cases of individuals infected with monkeypox have been detected in different parts of Europe and North America.

Circulation of the virus in people from different areas of the planet that have not travelled to endemic regions suggests the possibility of human dissemination through zoonotic contact with species that have the virus, thus facilitating subsequent horizontal transmission.⁶

Monkeypox virus is maintained in different animals that act as reservoirs and has primarily been identified in small rodents and non-human primates.¹⁰ Human infection can occur due to direct contact with the infected animal or due to exposure to fluids from the infected animal, such as blood. Infection can also occur through animal bites and, possibly, via the consumption of these animals associated with customs in rural communities in Africa.¹¹

Horizontal transmission between humans is the most common route of infection for the virus, mainly through contact with the skin lesions the infection causes, with secondary lesions due to autoinfection, and through contact with shared infected objects and areas.^{12,13}

Possible sexual transmission of monkeypox virus has been suggested based on the fact that the majority of the cases have presented in subjects without any history of travel to endemic areas and who have had close contact with symptomatic individuals. Characteristically, skin lesions are observed in the genital or perianal areas together with regional adenopathies.^{14,15} While more studies are still needed, it is possible for this route of transmission to occur (Fig. 2).

Clinical manifestations associated with monkeypox virus infection have been characterised by lasting approximately 2–5 weeks, with an estimated incubation period of 5–21 days.¹⁶ Signs and symptoms include: fever, headache, lymphadenopathy, myalgia, and skin manifestation such as macules, papules, vesicles and pustules which appear during a period of 5 days after the fever. Risk of infection is greater in the presence of skin lesions, however the possibility of transmission through asymptomatic individuals has not been ruled out.¹⁷

Monkeypox, unlike smallpox, has a mortality rate of less than 1%, which mainly affects children and young adults. Individuals with some immunodeficiency have been identified to be more vulnerable to developing more severe disease and thus present a higher case fatality rate.¹⁸

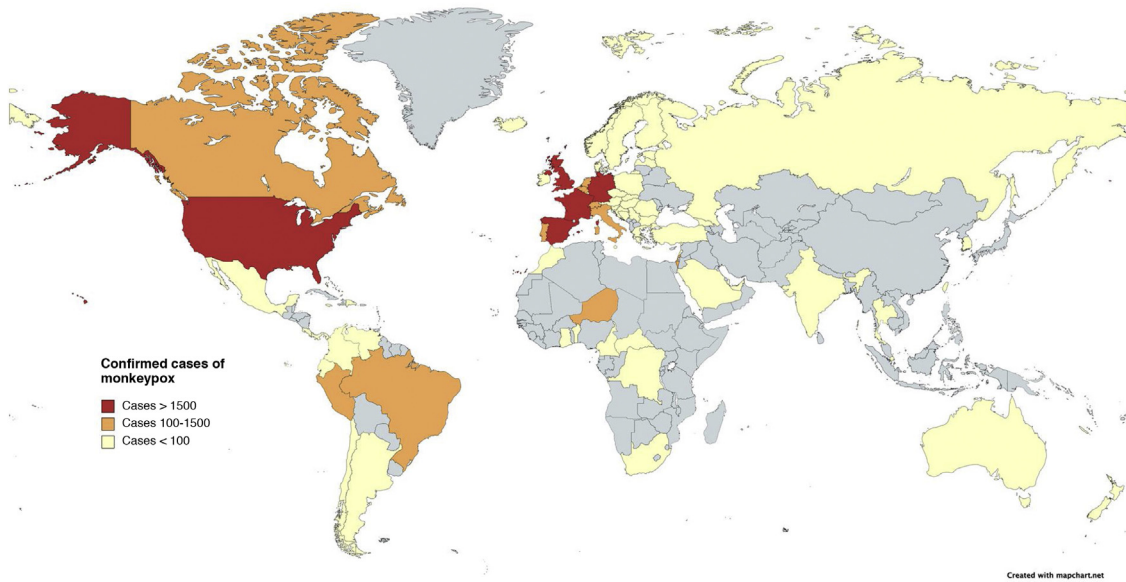


Figure 1 Map of confirmed cases of monkeypox since the first reported infections starting on 1 January 2022 up to 25 July 2022. Highlighted in red: United States, Spain, Germany, United Kingdom, and France, the countries most affected by virus transmission. In orange, those with a high chance of infection. In yellow, those with a low number of recorded cases. Made with <https://mapchart.net/world.html>.

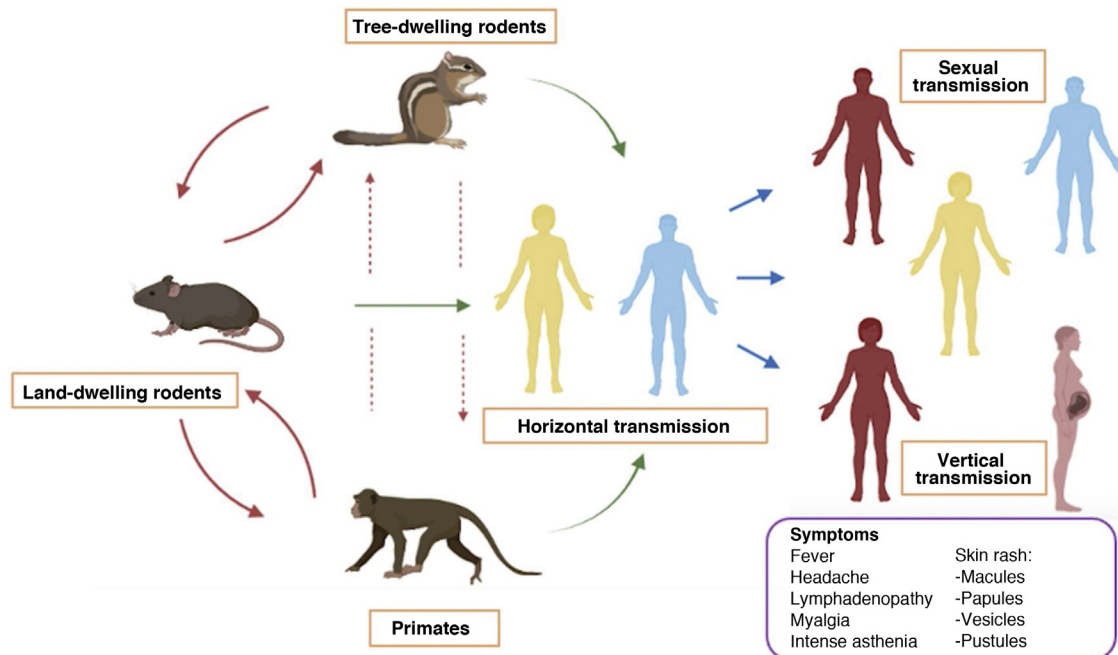


Figure 2 Transmission of the monkeypox virus. The natural reservoirs for the virus are thought to be tree- and land-dwelling rodents, where the virus is then transmitted between the rodents and non-human primates. It has been observed that these animal species are capable of transmitting and infecting humans through respiratory droplets, sexual transmission, contact with skin lesions and vertical transmission. The primary symptoms of monkeypox infection are fever, headache, myalgia, intense asthenia, and skin rash. The main difference from smallpox is the lymphadenopathy that the infection causes.

Evidence of monkeypox during pregnancy

We have limited information on the impact in pregnant women of infection with this emerging virus. In addition, the majority of the natural history of infection has occurred

in Africa in areas with social inequality, civil wars, and other social factors that limit potential monitoring or follow-up.¹⁹

Nevertheless, the few existing clinical studies have produced results that clearly show that monkeypox can be transmitted vertically.²⁰ The WHO reports vertical trans-

mission of monkeypox via the placenta, which can cause congenital infection, or infection can occur due to direct contact during or after birth (Fig. 2).²¹

The evidence supporting this idea has been established in an observational study in a cohort of 222 individuals admitted to a hospital in the Democratic Republic of the Congo: all the patients presented clinical signs and symptoms of monkeypox. Four pregnant women were identified during the study: three experienced foetal death and only one reached full-term and birthed a healthy baby.

Interestingly, among the gestational losses, two of the women presented with moderate-to-severe disease, which was associated with spontaneous miscarriage in the first trimester. The third woman, also with moderate-to-severe disease, in her 18th week of gestation, experienced intrauterine demise of the foetus. The foetus showed clear manifestations of monkeypox infection (cutaneous maculopapular lesions involving the trunk, head, palms and soles of the hands and feet); the presence of hydrops fetalis was detected, as well as hepatomegaly with peritoneal effusion. There were no congenital malformations nor was any damage to the placenta, foetal membranes, or umbilical cord observed. However, molecular testing identified virus DNA in foetal and placental tissue, confirming vertical transmission of the virus.^{22,23}

The study conducted by Jezek et al.²⁴ describes a probable, non-laboratory-confirmed case of perinatal monkeypox infection: a pregnant woman at 24 weeks' gestation with monkeypox infection who, after 6 weeks, delivered a premature infant that presented with generalized skin rash suggestive of the presence of the infection. Ultimately, the child died 6 weeks later of malnutrition (Fig. 3).

The clinical evidence has described the significance of the effect had by a member of the *poxvirus* most related to humans, such as the smallpox virus, which has greater morbidity and mortality among pregnant women as compared to women who are not pregnant.²⁵ As well, the effect of this infection within the perinatal context is related to a higher proportion of cases of preterm labour, premature birth and spontaneous abortion. Therefore, foetal deaths observed in monkeypox cases should not be considered an isolated event.²⁶

More clinical and experimental evidence is needed to understand the placental infection processes and how this can disrupt gestation and lead to foetal death.

With this review, we hope to shine a spotlight on the harm caused by viral infections during human gestation. It has already been shown how these pathogens play a significant role in disrupting the mother-baby pair, by producing an adverse clinical condition for the foetus, or damage to the placenta, caused by maternal infection, which culminates in the physiology of the pregnancy being affected.

Other emerging viruses, such as Zika, have shown that in-utero infections can be associated with congenital malformations and foetal neurological defects that result in poor quality of life for the neonate or even death.^{27,28} Vertical transmission of other pandemic viruses, such as SARS-CoV-2, remain a controversial topic. The clinical evidence has shown an increase in complications during gestation, such as the onset of pre-eclampsia, preterm labour, and foetal death.^{29,30}

Maternal infection can also lead to vascular and inflammatory lesions in the placenta that promote poor placental vascular perfusion and may be associated with the development of pre-eclampsia.³¹

While more studies are needed to understand the impact of SARS-CoV-2 infection during gestation, it is important to report this evidence to verify that these emerging viruses are pathogens that could potentially cause pandemics. Pregnant women must be considered a vulnerable population in light of these pathogens and, therefore, at-risk. The same is true for pregnant women and the novel monkeypox infection.

Recommendations for diagnosing and treating monkeypox during pregnancy

In terms of the general population, the recommendation is to avoid skin-to-skin contact with individuals with a skin rash that could be suggestive of monkeypox virus infection, to avoid contact with objects and materials that have been used by a monkeypox patient and, lastly, hand washing before eating and using the bathroom.^{21,32-34}

Likewise, the Centre for Disease Control and Prevention (CDC) has a series of recommendations for pregnant women. In the event that a woman has been exposed to the virus, she should be monitored for the appearance of symptoms. If symptoms do appear, the patient should isolate at home or in a health care setting depending on the severity of her symptoms. The differential diagnosis of the skin lesions may be broad at the start and include other sexually transmitted infections or skin rash infections. Patients should remain in isolation until all lesions have resolved, the scabs have fallen off, and a fresh layer of intact skin has formed.³⁵

Reproductive decisions should be reconsidered during monkeypox infection. While the evidence for the perinatal impact of this infection remains under study, pregnancy planning can be delayed until the risk of infection is minimal.³⁶

Again, experience with the COVID-19 pandemic has provided guidelines for being prepared and generating clinical and diagnostic algorithms that, together, help us improve care for pregnant women infected with monkeypox virus.

Dashraath et al.²¹ propose guidelines for monitoring pregnant women with monkeypox virus infection. The guidelines include clinical diagnosis based on the presence of compatible signs and symptoms, including sore throat or genital or anorectal pain, presence of regional lymphadenopathies and vesiculopustular rash, as well as recommendations for the diagnosis of biological samples (skin lesion exudates) via PCR. Differential diagnosis of the monkeypox clinical picture may also include infection by other pathogens such as varicella-zoster, herpes simplex, or syphilis.

If monkeypox virus infection is confirmed, isolation and hospitalisation in a health care setting with negative pressure rooms is indicated. Ultrasound foetal monitoring is advisable to identify anomalies such as foetal hepatomegaly or hydrops (Fig. 4).^{35,36}

There is currently no specific antiviral therapy for monkeypox infection in pregnant women. The United States Food and Drug Administration (FDA) has tested some antiviral drugs for the treatment of monkeypox infection.

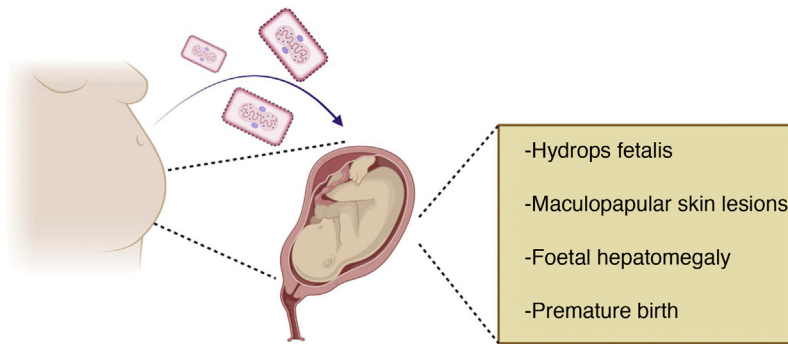


Figure 3 Vertical transmission. In the few studies of this infection in maternal-foetal setting, it has been shown that monkeypox virus transmission can cause clinical manifestations in babies such as hydrops fetalis, maculopapular skin lesions on the body, hepatomegaly, and premature birth.

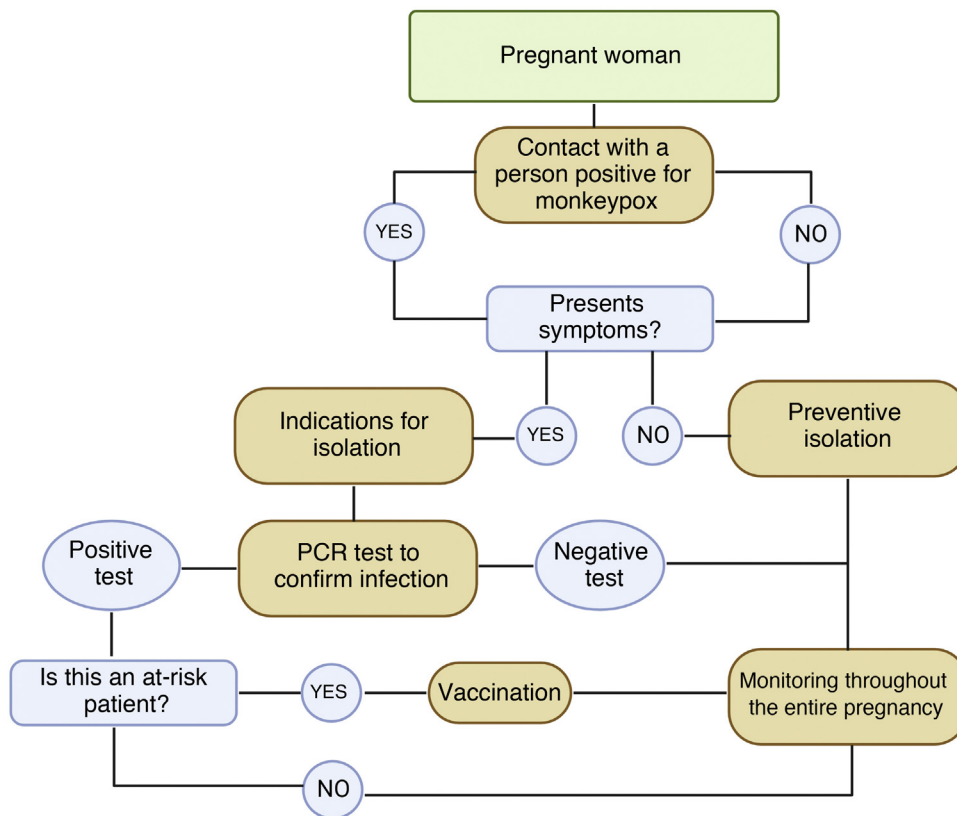


Figure 4 Clinical proposal for managing pregnant women with suspected monkeypox virus infection. Diagram of the management stages for pregnant patients with monkeypox virus infection or suspected infection and clinical follow-up that should be implemented in these cases to prevent complications with foetal development or the patient.

Tecovirimat, from SIGA Technologies laboratory, also recognised by the CDC, is an antiviral that inhibits orthopoxviruses by blocking the VP37 envelope wrapping protein. Currently there are no human data for its use during pregnancy: there are only two data on its impact in the gestational setting in animal models and with a dose that is 23 times higher than in humans, though no adverse effects were observed. Nevertheless, it can cause hypoglycaemia in patients with type 2 diabetes being treated with repaglinide. Tecovirimat is administered as one 600 mg capsule twice per day for 2 weeks, while the injectable presentation is rec-

ommended every 6 h for 2 weeks. Some adverse reactions have been reported for the oral route (at least 2% of tests in humans), with headache, nausea, abdominal pain, and vomiting; via injection, less than 4% presented with injection site reactions and headache.^{35–37}

Another drug alternative may be brincidofovir, an inhibitor that acts on the DNA polymerase of various bicatenary DNA viruses such as monkeypox. Nevertheless, administration of any of these drugs is only recommended when patients present severe complications.³³ Another option could be the administration of vaccinia immune

globulins, a cocktail of purified antibodies from individuals immunized with the smallpox vaccine. While there is no clear evidence regarding their efficacy for monkeypox infection during pregnancy, the use of immune globulins has been widely documented in other diseases during pregnancy, verifying their safety and efficacy.³⁸

Vaccination, a plan to prevent monkeypox infection during pregnancy

The safety and efficacy of vaccine use in pregnant women has been a topic of debate given that the majority of clinical studies do not include pregnant women. The few existing clinical studies have observed that vaccination during pregnancy has a dual beneficial effect: it prevents infection in the mother and protects the newborn.³⁹ Nevertheless, there are still risks, and the benefits and potential adverse effects must be assessed.⁴⁰

At present, pregnant women are one of the groups of interest during the recent monkeypox outbreak as it has been seen that vertical transmission is possible. Therefore, maternal vaccination should be considered as a way to control intrauterine infection.

The data generated by studies addressing the role of acquired immunization via vaccination against smallpox have shown that there is a protective effect against monkeypox virus infection, as clinical manifestations of the disease are prevented. The CDC currently recommends the use of two vaccines to protect against monkeypox: JYNNEOS (MVA-BN), a non-replicating viral vaccine of modified vaccinia Ankara, and ACAM2000, a second-generation vaccine derived from the live Dryvax virus.

In the case of MVA-BN, from the laboratory Bavarian Nordic, there is insufficient data in pregnant women to determine whether it presents a risk to this population group. No evidence of foetal demise was observed in animal models. It is administered via intramuscular injection in 2 doses (0.5 mL) with 4 weeks between each dose. Local reactions can appear following administration, such as pain at the injection site, redness, swelling, induration, and itching and systemic effects such as myalgia, headache, fatigue, nausea, and chills.⁴¹

On the other hand, the ACAM2000 vaccine, from Emergent Product Development Gaithersburg Inc. laboratories, is administered intradermally. One of the reactions that occurs 3 or 4 days after vaccination is the formation of a red blister that causes skin irritation. This blister ultimately turns into a scab that takes approximately 3 weeks to fall off.⁴² Administration of the replicating ACAM2000 vaccine is contraindicated in pregnant or breastfeeding women because congenital defects can occur in the foetus and infections can occur in the foetus or new-born. Therefore, women vaccinated with ACAM2000 are advised to not fall pregnant for 4 weeks or until the blister has healed and the scab has fallen off.⁴³

Therefore, pregnant women who have come into contact with monkeypox and are considered to be at risk are left with the option of vaccination with the JYNNEOS vaccine, with proven efficacy and protection against infection.^{34,44}

Conclusion

Monkeypox infection is currently considered a global health concern. Its spread across different countries has activated epidemiological warnings. In addition to immunocompromised patients, pregnant women are considered to be a vulnerable population group. This premise will help initiate protocols to prevent significant involvement of this population group.

Clinical evidence has suggested a strong possibility of vertical monkeypox infection during pregnancy, which can cause considerable foetal harm and the potential for fatal outcomes. Some health care strategies, such as social distancing, the use of protective equipment, and reproduction planning, may help prevent infection among this population.

Vaccination of pregnant women in risk settings should be considered as a prophylactic measure that will help ensure a safe gestation.

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Conflicts of interest

All the authors declare that they do not have any conflicts of interest.

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