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Monkeypox in pregnancy: clinical recommendation by the World Association of Perinatal Medicine-WAPM and the Perinatal Medicine Foundation-PMF

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Abstract

The World Health Organization in May 2022 declared the monkeypox virus (MPXV) a health emergency. Since then, over 45,355 cases have been reported, mostly from countries where the disease is not endemic. At the moment, most confirmed cases with travel history are reported to countries in Europe and North America, rather than West or Central Africa where the monkeypox virus is endemic. Its transmission depends on large respiratory droplets and skin-to-skin or skin-to-lesion close physical contact, including oral, anal, and vaginal intercourse therefore, women are also at risk of acquiring it. Given few data available, women's and clinicians' concerns about the uncertainty of the clinical course and management are more than understandable, especially so after the SARS-CoV-2 pandemic. Lessons must be learnt from our prior mistakes and pregnant individuals should be included in international registries as well as any studies evaluating new treatments or vaccines. The following recommendation aims to provide the latest evidence about the effect of MPXV in pregnancy as well as recommendations for clinical management.

Keywords: Monkeypox, pregnancy, management.

Introduction

In May 2022, the World Health Organization declared the monkeypox virus (MPXV) a health emergency. Since then, over 45,355 cases have been reported, mostly from countries where the disease is not endemic.[1] At the moment, most confirmed cases with travel history are reported to countries in Europe and North America, rather than West or Central Africa where the monkeypox virus is endemic.[2]

Although it initially presented in non-endemic countries as a disease affecting mostly men who have sex with men (representing up to 90% of the affected population), it has been demonstrated that its transmission is not determined by gender nor by sexual intercourse. Its transmission depends on large respiratory droplets and skin-to-skin or skin-to-lesion close physical contact, including oral, anal, and vaginal intercourse therefore, women are also at risk of acquiring it.[3]

Unlike the new SARS-CoV-2, MPXV was first isolated last century being the first human case diagnosed in 1970,[4] although the data is limited as it was endemic

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in West and Central Africa where medical reporting is scarce. Nevertheless, there is some knowledge about its risks and a few cases have been reported in pregnant women including information about the risk of transmission to the offspring.[5] Given few data available, women's and clinicians' concerns about the uncertainty of the clinical course and management are more than understandable, especially so after the SARS-CoV-2 pandemic. Lessons must be learnt from our prior mistakes and pregnant individuals should be included in international registries as well as any studies evaluating new treatments or vaccines.

The following recommendation aims to provide the latest evidence about the effect of MPXV in pregnancy as well as recommendations for clinical management.

Monkeypox: the Virus

MPXV is a double-stranded DNA zoonotic virus of the Orthopoxvirus Poxviridae family, which includes others such as the variola virus (responsible for smallpox), vaccinia virus (used in the smallpox vaccine) or the cowpox virus. It was given this name as it was first identified in monkeys in 1958 although its main hosts are rodents.

The MPXV can be categorized into two major groups: the Congo Basin (clade I) and West African (clades II [formerly clades 2 and 3]).[6] Laboratory findings suggest that the current outbreak is due to the West African clade, more particularly to clade IIb, which has a case fatality rate of around 1–3%,[7] whereas the Congo Basin presents with more severe disease, with up to 10% mortality.[6] It is important to note that mortality in different settings may differ substantially. Clade IIb was already responsible for outbreaks in North Africa in 2007 and 2008 with some cases exported to Europe.[8]

Transmission can be both animal-to-human and human-to-human. In the first case, it can happen via bite or direct contact with the blood, meat, or lesions of an infected animal. In the second scenario, the transmission of MPXV occurs through large respiratory droplets, direct lesion-to-skin contact, and contaminated fomites. There is few evidence of household spread of any form of monkeypox (0–11% of close contacts mostly in those unvaccinated against smallpox), suggesting that it requires prolonged or repeated exposure to virus-shedding lesions.[9] Similarly to other poxviruses, MPXV replicates at the site of inoculation and subsequently spreads to locoregional lymph nodes before becoming systemic through the bloodstream.

Regardless of the exposure route, primary viremia occurs after 7 days and until 14 days of infection (range: 5–21 days) corresponding with the incubation period. A second viremia initiates thereafter as a consequence of further viral replication starting the prodromal phase characterized by the onset of fever, headaches, myalgia, fatigue, or lymphadenopathy. Skin lesions appear 1–3 days after the onset of fever as MPXV seeds the skin and mucous membranes with virions at various stages of assembly. This causes an enanthem and skin exanthem evolving from macules to papules, vesicles, pustules, and crusts. The risk of transmission will remain from the onset of fever until the resolution of crusts.[10] A summary of the viral infection course is presented in **Table 1**.

Recommendation

- In summary, MPXV is a DNA virus with two molecular profiles, being clade II (case fatality rate of 1%) responsible for the current outbreak. It can be transmitted by large respiratory droplets or skin-to-skin contact. The infectious period lasts until the resolution of crusts.

Clinical Course

At 15 to 18 days after infection, a prodromal period consisting of fever, sweating, myalgia, headache, and

Table 1. Monkeypox infection course.

	Infection	Primary viremia	Secondary viremia	
Clinical feature	Asymptomatic	Asymptomatic	Fever, sweating, myalgia, headache, fatigue	Skin lesions
Day (mean)	0	7–14	15–18 (lasts for 2–5 days)	21–35
Day (range)	0	5–21	12–24 (lasts for 2–5 days)	15–42

Table 2. Monkeypox severity based on skin lesions according to WHO criteria.

Severity	N° skin lesions
Mild	<25
Moderate	25–99
Severe	100–250
Very severe	>250

lymphadenopathy will last for approximately 2 days. Large inguinal or cervical lymphadenopathies are very characteristic in monkeypox, although they have not been reported in more than half of the newly diagnosed cases. Three days after the onset of fever, a rash affecting the face and extremities will appear, with lesions progressing from macules, papules, vesicles, pustules, and finally, crusts. Skin lesions can be graded using the WHO classification based on smallpox (**Table 2**). As with other poxviruses, other manifestations include pneumonia (12%), ocular complications (4–5%), encephalitis, and secondary soft-tissue infections.

Atypical features of the ongoing outbreak are a high rate of genital, perianal, and oral lesions and rash that does not evolve synchronously, including an erythematous maculopapular rash of rapid onset separate from areas of vesicles or pustules. Furthermore, a high proportion of patients present with symptoms without a prodromal phase. Common signs and symptoms of all MPXV and the current Clade IIb are presented in **Table 3**.[11]

Table 3. Signs and symptoms of monkeypox.

	All MPXV[1]	Current strain[3]
Fever	87–99%	62%
Myalgia	95%	31%
Headache	90%	27%
Lymphadenopathy	69–98%	90%
Cervical	85.6%	-
Inguinal region	77.3%	-
Mouth/Throat	28.3%	-
Skin lesion / rash	96.8%	95%
Anogenital rash	-	73%
Solitary genital ulcer	-	10%

MPXV: monkeypox virus.

Recommendation

- A prodromal phase 7–14 days after infection precedes the onset of skin lesions (although this only was reported in 60% of current cases). Skin lesions (particularly genital) and lymphadenopathy are currently the most common presentation.

Diagnosis

Diagnosis must take into account epidemiological, clinical, and laboratory data. Diagnosis should be suspected in cases that present with suggestive clinical symptoms and also an indicative epidemiological background.

Clinical

Patients presenting with lymphadenopathy and/or vesiculopustular rash, including rash localized to the genital region, especially after a prodromal phase of fever or myalgia.

Epidemiological

Regardless of travel to endemic zones (mainly Central or West Africa) within the last 21 days, epidemiological suspicion should arise if the patient has had close contact with individuals who have suspected or confirmed monkeypox. Furthermore, this should apply if they are part of a social network experiencing monkeypox activity or after exposure to exotic pets.

Laboratory

Diagnosis can be established both by PCR testing of viral lesions or serological blood test being PCR testing more reliable given its higher detection rates as viremia is highest at skin lesions. Samples should be collected as follows:

- **DNA detection with PCR:**[12] Skin lesions should be swabbed vigorously, preferably from open lesions or the surface of a vesicle. If there are different areas affected, it is recommended that more than one area is tested by taking more than two swabs for each region. Throat swabs can be performed in cases without skin lesions (either symptomatic or after contact with a positive case), but their detection rates are much lower.
- **IgM detection with serological analysis:**[13] Patients with monkeypox typically have detectable levels of anti-orthopoxvirus IgM antibody during the period of 4 to 56 days after rash onset.

Differential diagnosis should include other exanthematous diseases such as varicella, herpes virus, or smallpox.

Recommendation

- Diagnosis should be suspected by epidemiological and clinical features and is best confirmed by PCR testing of skin lesions rather than serological IgM determination.

Pregnancy

Special concerns for pregnant women

Data on MPXV in pregnancy are limited. There is an overall concern with the current MPXV variant which seems to have accumulated more polymorphisms than ever before.[14] Furthermore, the discontinuation of smallpox vaccination puts non-vaccinated individuals at significant risk of acquiring monkeypox since they lack cross-protective immunity. Some authors argue for an even higher hypothetical risk in pregnant women based on the physiological immune changes during pregnancy (with lower Th1 lymphocytes and increased Th2) which inherently make these women more susceptible to viral infections.[15]

Considering other poxviruses like smallpox, one could extrapolate that MPXV could carry a high risk of severe congenital infection, pregnancy loss, and maternal morbidity and mortality.[16] All in all, there is very limited data on MPXV in pregnancy as it is subject to reporting bias as well as it being endemic to low-middle income countries where medical reporting is not as common. There is even fewer data on the current variant, although international registries have been developed which will hopefully shed some light in a near future.

There seems to be a risk of vertical transmission as well as contact transmission during birth. A cohort study[5] conducted between 2007 and 2011 in the Democratic Republic of Congo (DRC) included four pregnant women with laboratory confirmed MPXV. Three women with moderate/severe maternal infection had adverse obstetric outcomes: two first-trimester miscarriages and one had a second-trimester loss at 18 weeks of gestation. This fetus had common signs of the virus including a vesicular rash, hepatomegaly, and hydrops with a high viral load detected in fetal tissue, umbilical cord, and placenta – confirming vertical transmission of MPXV. The fourth reported woman had a different clinical course with milder symptoms and delivered a neonate at term with no clinical features of monkeypox infection.

In another report[17] of a probable (non-laboratory-confirmed) case, a woman infected at around 24 weeks of gestation delivered preterm at 30 weeks. The baby also presented with signs consistent with the infection, with a skin rash, and died of malnutrition 6 weeks later.

Although not confirmed, given that these cases are reported from the DRC, it would be safe to assume that they were caused by the Congo variant, the more virulent one which has not been responsible for the current outbreak. All in all, from a pregnancy standpoint, few available data seem to indicate that pregnancy course could depend on maternal severity and that vertical transmission as well as contact transmission during labor are plausible.

Pregnant women could have a higher susceptibility to MPXV infection. In those with severe maternal features, vertical transmission has been reported with severe fetal sequelae including morbidity and mortality. However, this risk is not quantifiable given that there are few reports and probably was based on a more severe variant (clade I).

Prevention

As with any other medical condition, prevention is key. High-risk contacts should undergo self-isolation until proven negative and if symptomatic, a 21-day isolation period is warranted until another cause is found. Confirmed cases should undergo self- isolation during the most infectious period, that is, from the onset of fever until the resolution of the skin lesions.[18]

Vaccination

Individuals vaccinated for smallpox seem to be protected from MPXV through cross- protective immunity. However, women of reproductive age are not likely to be vaccinated given the discontinuation in the 1980s.[19] There are already two available MPXV vaccines. The modified vaccinia Ankara (MVA), from a highly attenuated virus, and the ACAM2000 vaccine, a replication-competent vaccine. The MVA vaccine has shown efficacy of up to 85% and has been associated with lower side effects than the ACAM200, ergo it should be the first-line option.[20]

Sadly and with history repeating itself again, none of these vaccines have been approved for their use in pregnancy. Nevertheless, the MVA is developed from

a non-replicating virus so no adverse effects should be expected. Furthermore, there are some available reports which show no adverse outcomes in vaccinated pregnant women.[21]

MVA should be considered safe during breastfeeding as it is unlikely that the virus is eliminated through breast milk.[22]

Recommendation

- WAPM recommends caution and discussing the possible benefits and risks with pregnant patients regarding the low prevalence of MPXV at the moment. In those with other risk factors or highly prevalent areas, the preferred vaccine at the moment is the modified vaccinia Ankara (MVA).

Post-exposure prophylaxis

Post-exposure prophylaxis should be considered in those at higher risk of contracting the disease, that is those in direct contact with a known confirmed case during the shedding stage. Extrapolating from smallpox, immunocompromised individuals, pregnant women, and children are at highest risk of developing the most severe forms of the disease.

Prophylaxis has been studied both by administration of the MVA vaccine as well as vaccinia immune globulin (VIG).

The use of the MVA vaccine seems to reduce the symptoms of the disease. Therefore, many health institutions have established a recommendation to offer the MVA vaccine in non-pregnant individuals ideally within the first 4 days after a confirmed contact. If administered between days 4 and 14, vaccination is thought to reduce the symptoms of disease but not prevent it. Peak immunity is expected at 14 days after the second dose of vaccine.[20,22] The value of the MVA vaccine in pregnant women is still controversial.

The use of VIG (purified antibodies after immunization with the smallpox vaccine) has been shown to be less effective and therefore second line is restricted to those who cannot have MVA.[23]

Post-infection protective measures

Individuals who test positive for MPXV should be considered infectious until all lesion scabs fall off and re-epithelialization occurs, which typically lasts two to four weeks. Self-isolation is recommended for at least 21 days.

Condom use during any sexual activity should be recommended for 12 weeks after recovery.[24]

Recommendations

- WAPM recommends discussing patients with highest risk of infection, that is with a confirmed positive contact and skin-to-skin or large respiratory droplet exposure, about the possibility of post-exposure prophylaxis. In those at highest risk, the preferred treatment is the modified vaccinia Ankara (MVA), especially within the first 4 days. Regardless of high-risk contacts, those with other high risk factors in high prevalence settings should be informed about the possibility of immunization with MVA.
- After confirming infection, isolation should be recommended considering that the person remains infectious until all lesion scabs fall off. Condom use during any sexual activity should be recommended for 12 weeks after recovery.

Treatment

The majority of MPXV cases, especially those with Clade IIb, will only have mild forms of the disease and not require medical treatment.

Skin lesions do not require specific treatment and counseling should focus in avoidance of scratching and keeping them clean in order to avoid secondary bacterial infection. It is best to keep the exanthem open to air dry rather than cover it. Skin debridement should not be performed unless done by an expert wearing appropriate personal protective equipment.[24]

Those with moderate or severe forms or at highest risk of progression may require antiviral treatment. High risk patients have been described by epidemiological (high risk factors), clinical and laboratory findings (severity features) as presented in **Table 4**.[24]

Currently, there are no specific antiviral drugs for MPXV but tecovirimat, cidofovir/brincidofovir, and trifluridine+tecovirimat may be considered.[25] Tecovirimat is the treatment of choice by most societies, although some experts may suggest dual therapy with tecovirimat and cidofovir in patients with severe disease.

- **Tecovirimat:** licensed for the treatment of smallpox, MPXV, cowpox, and complications from immunization with vaccinia. It can be administered both orally and intravenously and adjusted for patients' weights. The most frequent posology is twice daily for 14 days.[26]
- **Cidofovir:**[27] approved for the treatment of cytomegalovirus. It inhibits replication of MPX and is administered intravenously. It has shown activity against poxviruses in laboratory and animal studies.

Table 4. Severity features of MPXV.

Epidemiological	Children <8 years old, pregnant women and immunosuppressed patients. There is low evidence supporting that patients with chronic skin conditions such as atopic dermatitis or acute skin conditions may also be at higher risk for complications, such as bacterial infection.
Clinical	WHO classification > mild disease. Nausea/vomiting, painful cervical lymphadenopathy causing dysphagia, poor oral intake, eye pain, vision abnormalities, hepatomegaly, sepsis, dehydration, respiratory distress/pneumonia, and/or confusion.
Laboratory	Elevated hepatic transaminases (AST and/or ALT), low blood urea nitrogen, low albumin, elevated white blood count or low platelet count.

Brincidofovir[28] is an analog of cidofovir approved for the treatment of smallpox and can be administered orally. It is not recommended in pregnancy due to fetal toxicity,

- **Trifluridine:**[29] approved for the treatment of ophthalmic herpes. Off-label use of it has been proposed for eye abnormalities. Drops or ointments can be applied every four hours for 7 to 10 days.

Recommendation

- In summary, WAPM recommends discussing with patients, especially those with more than moderate disease or any severity features, about the possibility of antiviral treatment with tecovirimat. Those with eye lesions could opt for the off-label use of trifluridine.

Proposed clinical management by WAPM/PMF

The majority of MPXV cases, especially those with Clade IIb, will only have mild forms of the disease and not require medical treatment.

Diagnosis

In any pregnant woman with clinical signs or symptoms of MPXV infection and a suggestive epidemiological background, testing is warranted. This can be done by a swab of a skin lesion if it is present or an oropharyngeal swab and blood sample for serology if the patient presents with fever and systemic symptoms without skin lesions. Those with a confirmed contact but not presenting any symptoms should undergo an oropharyngeal swab.[30]

Management of infection

After a high-risk contact, the possibility of MVA vaccination as post-exposure prophylaxis should be offered. Furthermore, close follow-up and PCR testing should be done to exclude infection. Negative asymptomatic cases can resume normal activity whereas symptomatic cases, even if negative, should undergo isolation until another cause is found or until 21 days have elapsed. Pregnant individuals with confirmed MPXV infection should be managed by a multidisciplinary team. Careful physical examination, chest X-ray, complete blood count, and biochemistry including liver enzymes and coagulation should be evaluated.

Risk assessment should be performed and the possibility of treatment with tecovirimat should be discussed with the patient as pregnancy itself is a hypothetical risk factor for severe disease. Mild cases presenting solely with mild skin lesions according to WHO, without any other risk factor, can be managed outpatient with telephone follow-up and patient self-monitoring.

Those with moderate criteria or any other risk factor should be hospitalized for follow-up until further evidence of MPXV infection course in pregnancy is determined. During hospitalization, treatment with tecovirimat should be offered, antibiotic treatment should be considered for avoiding bacterial superinfection, and close maternal monitoring should be conducted. Given the possibility of fetal vertical transmission and a higher risk of preterm birth, fetal surveillance with cardiotocography at least once daily during hospital admission is warranted after viability is considered. Cervical length measurement should be considered as well given the hypothetical higher risk of preterm birth. Furthermore, fetal maturation with antenatal corticosteroids should be considered at least until 34 weeks.

Pregnancy follow-up

Women with outpatient management should be offered telephone visits until the infectious period elapses. If that is not an option or the visit can solely be done in-hospital (i.e. anomaly scan at the adequate gestational age), the personnel should wear appropriate protective equipment including personal protective equipment.

Vertical transmission has been described in MPXV and therefore, until further evidence arises, it seems prudent to recommend fetal monitoring during the acute episode if the woman requires hospitalization and further follow-up until resolution.

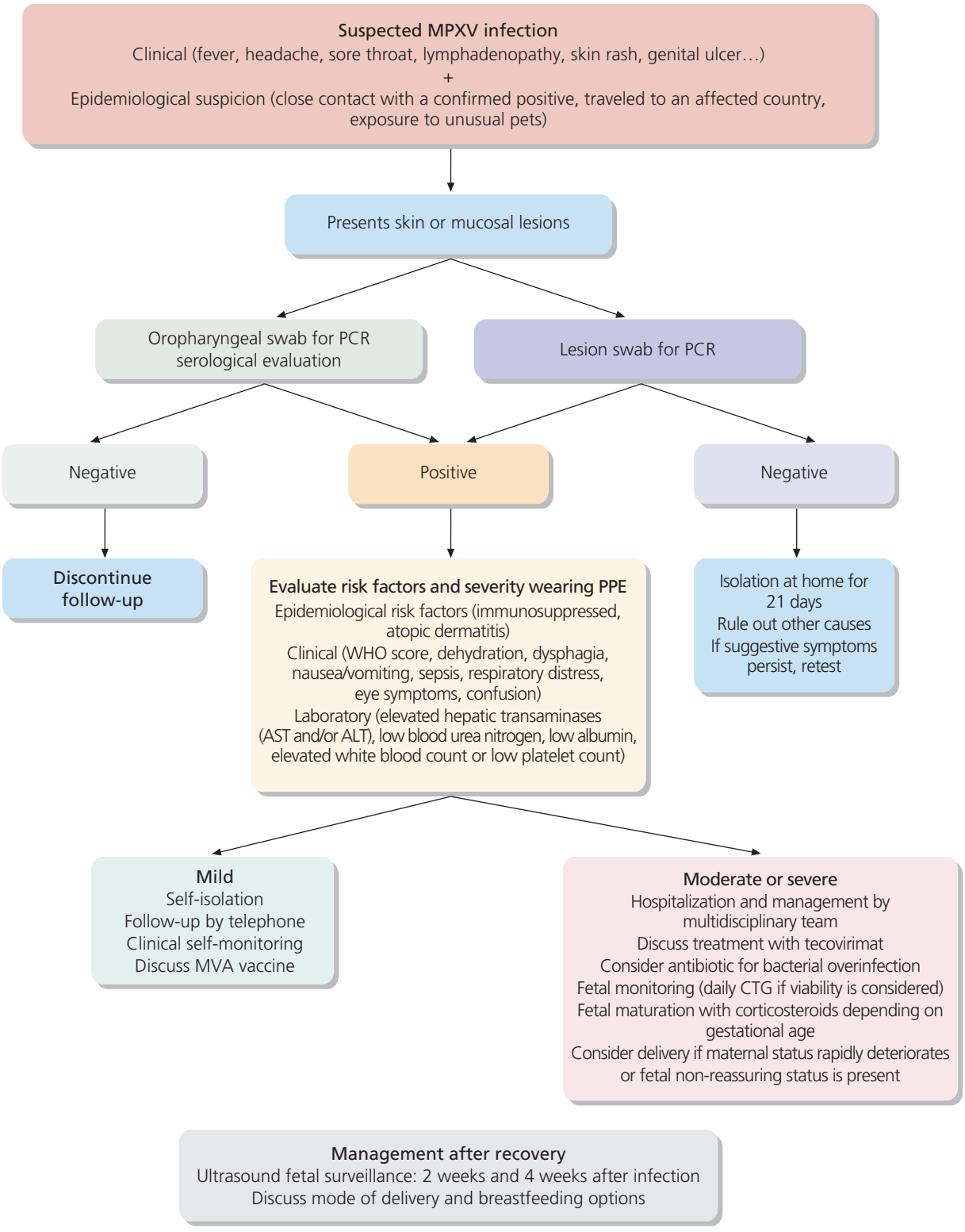

Fig. 1. Algorithm for management of suspected MPXV infection.

A sonographic evaluation 2 weeks after the onset of symptoms and 4 weeks later is a reasonable approach and further monitoring can be established based on ultrasound findings. Fetal evaluation should target fetal biometry and Doppler study, detailed anatomic (especially liver and neurosonographic features), and placental evaluations.

Regarding the mother, there are no specific concerns after the resolution of symptoms and recommendations should be the same as with those non-pregnant cases.

The timing of delivery should not be modified due to MPXV infection except in severe cases with maternal or fetal compromise considering gestational age and estimated fetal weight. Conditions should be optimized considering the use of antenatal corticosteroids and magnesium sulfate according to local protocols. Regarding the mode of delivery, women with active genital lesions should be counseled about the possibility of performing a cesarean section in order to avoid contact transmission given that neonates are at the highest risk of severe disease. However, they should be informed that as there is a risk of vertical transmission during pregnancy, neonatal infection may not be precluded. Furthermore, even in absence of genital lesions, a cesarean section could be offered as MPXV has been detected in vaginal fluid.

Neonatal care, rooming in, and breastfeeding

The neonate should have a complete full exam looking for clinical signs of MPXV infection. PCR testing of swab samples from the throat or any skin lesions should be done as with any high-risk contact. Isolation from the mother is recommended especially during the infectious period and personnel should wear protective equipment until a negative status is confirmed. If the neonate tests positive, it is advisable that they stay together.

Regarding breastfeeding, risks and benefits should be evaluated in terms of the setting (high-middle vs low-income countries). When possible, it would seem advisable that positive women with negative MPVX children do not breastfeed. However, breastfeeding should not be contraindicated in cases where both are positive.

Recommendation

A summary of management recommendations is presented in **Fig. 1**.

Finally, WAPM encourages active participation in the collection of robust data in this setting to improve the knowledge and ultimate care of women and children.[31,32]

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