Guía de práctica clínica

GUÍA DE PRÁCTICA CLÍNICA VIRUELA SÍMICA Y EMBARAZO: EL RESURGIMIENTO DE UN VIEJO CONOCIDO

Mauricio Herrera Méndez[1], Mario Alfonso Rebolledo Ardila[2], Nicolás Alejandro Torres Montañez[3], Yaisa Maritza Castaño Toro[3], Yomayusa, Nancy[4], Álvarez-Moreno, Carlos Arturo[5]

1 Head Chief of the Maternal Fetal Medicine Department – Obstetrics Department–Clínica Colsanitas, Clinica Universitaria Colombia, Clinica Pediatrica–President of the International Foundation of Maternal Fetal Medicine.
2 Clinical Coordinator of Maternal fetal Medicine – Maternal Fetal Medicine Department–Clínica Colsanitas
3 Second year Fellow Maternal Fetal Medicine – Departamento de Medicina Materno Fetal–Clínica Colsanitas
4 Grupo de Investigación Traslacional–Instituto Global de Excelencia Clínica Kerality – Fundación Universitaria Sanitas
5 Médico especialista en Infectología y epidemiologia Clínica.Profesor Titular, Enfermedades Infecciosas, Departamento de Medicina Interna, Facultad de Medicina, Universidad Nacional de Colombia.Vicepresidente Científico, Clínica Colsanitas, Grupo Keralty.Miembro, Academia Nacional de Medicina de ColombiaMiembro honorario, Sociedad Americana de Enfermedades Infecciosas (FIDSA)

RESUMEN

Introducción: La viruela símica es una zoonosis asociada al contacto con animales, originaria y endémica en países de África Central. En julio de 2022 se reporta un brote mundial que concentra la mayoría de los casos en países fuera de África como Estados Unidos, España, Alemania y el Reino Unido. El embarazo es considerado una condición de riesgo, y se asocia con desenlaces tales como aborto espontáneo, parto pretérmino y óbito fetal. Su adecuado diagnóstico, manejo y seguimiento disminuye la probabilidad de desenlaces maternos y perinatales adversos. Es por eso que consideramos necesario crear una Guía de Práctica Clínica basada en la mejor evidencia disponible desde la medicina materno fetal. **Metodología:** Se realizó una búsqueda de la literatura con metodología sistemática en las bases de datos MEDLINE, Embase, LILACS, Google Scholar y Web of Science. Luego de aplicar los filtros correspondientes se incluyeron un total de 11 artículos. Se incluyeron adicionalmente otros artículos encontrados de forma no sistemática dada su importancia y relevancia para la realización de la guía. **Resultados:** Hasta la fecha sólo se han reportado 7 casos de infección por viruela símica en el embarazo. El resultado final de los embarazos sólo fue satisfactorio en uno, mientras que los otros presentaron aborto espontáneo, óbito fetal, parto pretérmino y muerte neonatal temprana. La alta sospecha diagnóstica es esencial para un adecuado abordaje de la paciente obstétrica. El diagnóstico mediante PCR específica para viruela símica

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Correspondencia: maurioherreram@gmail.com

ha mostrado un adecuado rendimiento en múltiples series. El tratamiento con antivirales e inmunoglobulina intravenosa en el embarazo parece ser el primer paso en el manejo de síntomas y reducción de la transmisibilidad. Una adecuada clasificación de la severidad permitirá definir las pacientes embarazadas susceptibles de ser vigiladas de forma intrahospitalaria y las que pueden ser aisladas en su domicilio con estandarización de los patrones de seguimiento del bienestar fetal. **Conclusiones:** La viruela símica es una zoonosis emergente que puede complicar el embarazo, el parto y el puerperio, así como aumentar los riesgos de complicaciones maternas y perinatales. Un adecuado diagnóstico, clasificación, manejo y seguimiento permitirán mejorar la probabilidad de éxito en la población gestante.
Palabras clave: Viruela; Mono; Monkeypox; Embarazo; Atención perinatal; Guía

CLINICAL PRACTICE GUIDELINE MONKEYPOX AND PREGNANCY: THE RESURGENCE OF AN OLD ACQUAINTANCE

SUMMARY

Introduction: Monkeypox is a zoonosis associated with contact with animals, which is original and endemic in countries around Central Africa. In July 2022 a global outbreak was reported, with most of the cases presented in countries outside Africa like the USA, Spain, Germany, and the United Kingdom. Pregnancy is considered as a risk condition, associated with outcomes like spontaneous abortion, preterm birth, and fetal demise. An adequate recognition, diagnosis, management, and tracing diminishes the risk of maternal and perinatal adverse outcomes. Therefore, we considered it necessary to create this Clinical Practice Guideline based on the best available evidence from Maternal Fetal Medicine. **Methodology:** A systematic search was performed in databases (MEDLINE, Embase, LILACS, Google Scholar, Web of Science). After filtering, we finally included 11 articles. Additionally, some other articles found in a nonsystematic search were included given their importance and relevance to achieve this guideline. **Results:** Until the drafting of this guideline, only 7 cases of monkeypox infection have been reported in pregnant women. The result of these 5 pregnancies was successful only in one; meanwhile, the remaining 4 cases resulted in spontaneous abortion, fetal demise, preterm birth, and early neonatal death. A high clinical suspicion is essential for an adequate approach in the obstetric patient. The PCR for the diagnosis of monkeypox has shown a high sensibility in multiple series. The antiviral treatment and the intravenous immunoglobulin in pregnancy seems to be the first step in the treatment of symptoms and reduction of transmission. A clear classification for the severity status will allow the clinician to make the right choices around the time of tracing and the place for isolation, with the standardization of the fetal wellbeing follow up. **Conclusions:** The monkeypox is an emergent zoonosis that can complicate the pregnancy, the labor and the postpartum, as well as increase the risk of maternal and fetal adverse outcomes. An adequate diagnosis, treatment and tracing will improve the probability of success in pregnant women.
Keywords: Smallpox; Monkeypox; Monkey; Pregnancy; Perinatal care; Guideline.

INTRODUCTION

In July 23 2022, the World Health Organization (WHO) decreed the infection by Monkeypox virus as a global emergency, after the outbreak presented in Africa during May 2022. This outbreak spread fast and progressively to more than 72 countries worldwide, with over 10.000 cases reported (1). The Monkeypox infection is a zoonosis caused by the Monkeypox virus, from the Orthopoxvirus family, where viruses like Variola virus (smallpox) also belong. It was identified for the first time in 1958 in monkeys and the main host are rodents (2-4). Currently, there have been reported a total of 7 cases of monkeypox infection in pregnant women: 2 in Nigeria, 4 in the Democratic Republic of Congo and one in Zaire, none during the present outbreak (5-7). At the time, there were not clear recommendations around pregnant women; this is why we made this Clinical Practice Guideline based on the best available evidence.

METHODOLOGY

Protocol, sources of information and literature search

A systematic search was performed in the databases MEDLINE, Embase, LILACS, Google Scholar, Web of Science). We found a total of 49 publications which were filtered by year, language, title and abstract. After filters, we had a total of 11 studies. Additionally, some other articles found in a nonsystematic search were included given their importance and relevance to achieve this guideline. Information available in the WHO and CDC website was also included.

Data extraction

The extracted data for the present guideline included the data of the authors and the year of publication. The data was assessed in an independent manner by two authors of the guideline (YC, NT)

RESULTS

Historical review and current scene in Public Health

After implementing the worldwide vaccination program for the eradication of smallpox, which concluded in the 70´s, the cross protection offered by that vaccine for other pox viruses has been lost. The first case of. Monkeypox was reported in 1970 in Democratic Republic of Congo, and since then it has become an endemic disease at Western and Central Africa. In 2017, it was reported a monkeypox outbreak in Nigeria that spread and persisted until today (2).

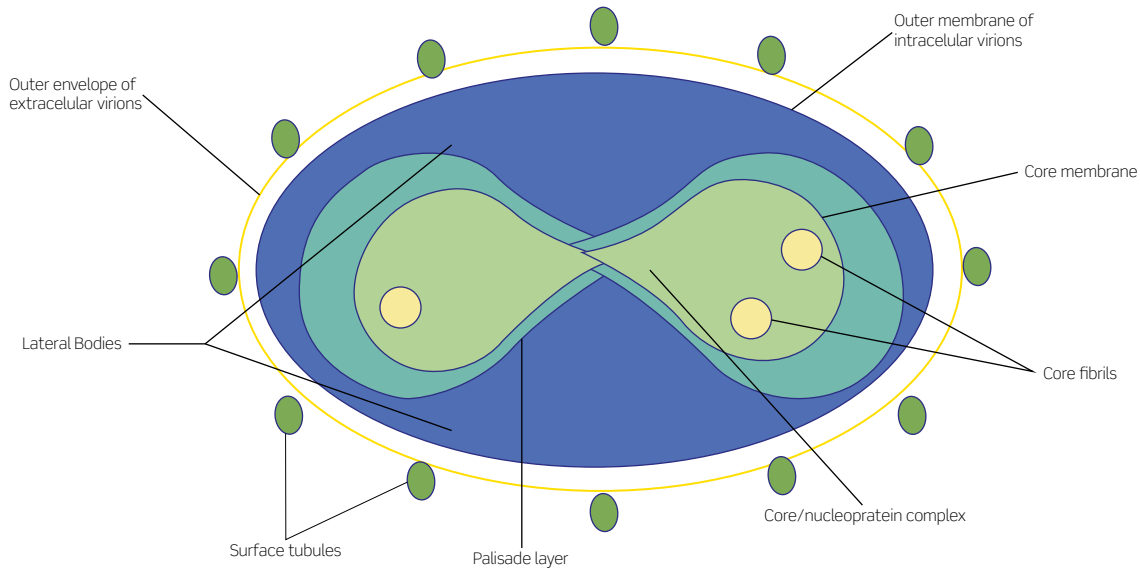
The first non-African outbreak occurred in 2003 in the USA and was associated with contact with prairie dogs, which acquired the infection after contact with small rodents coming from Ghana, where the monkeypox is endemic. After this interaction, the arrival of the virus was a matter of time. The virus was detected at six states inside the USA, resulting in 47 cases, all of them associated with contact with animals. Since then, until now, only 2 cases inside the USA have been reported, both with history of traveling to Nigeria (3).

On May 17 2022, it was reported the first case inside the USA with isolation of the western African variant of an immigrant from Canada. After two months the outbreak spread and a total of 556 cases were reported with the isolation of the same variant. Fortunately, no deaths were reported and none of those cases occurred in the pregnant population (3). In the USA, as well as in the other countries outside Africa, the clinical presentation is atypical. Recent cases have been reported in countries were the monkeypox is not endemic. (3)

Monkeypox: virus biology

The poxvirus belongs to the poxviridae family, which is divided according to the definitive host into the Chordopoviridae and the Entomopoxviridae. With similar characteristics to other Orthopoxvirus, the Monkepox virus has a size of 200-250 nm. The morphology of the

FIGURE 1. *Structure of the virus.*



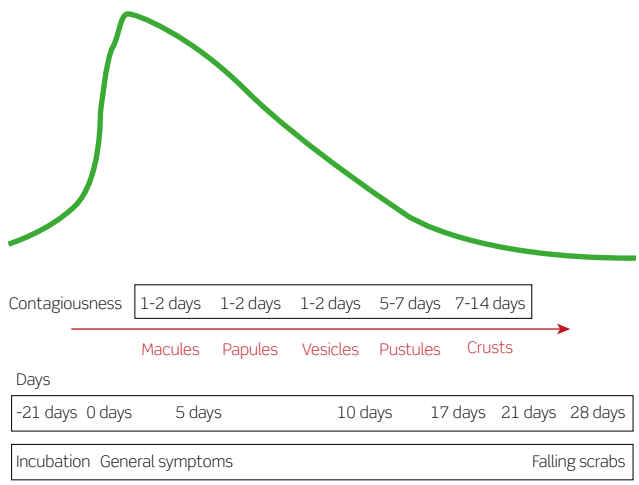
Adapted from: https://vitrosens.com/what-is-monkeypox-virus/

virus shows that the virions are ovoid, enclosed in an external membrane of lipoproteins, with a biconcave core, with a lateral body at each side. This core contains enzymes, a double stranded DNA genome by multiple transcription factors that allows the virus the replication inside the host cells (Figure 1) (8).

Natural history of the infection and clinical manifestations.

The mean time between the contact with virus and the onset of signs and symptoms is 5 to 13 days (9,10). The time of incubation occurs between 6 and 13 days, followed by a prodromal phase characterized by fever, sweats, headache, myalgia, and fatigue. Subsequently the rash starts 1 to 4 days after the onset of the fever and can have a duration up to 4 weeks. This can affect the face and extremities, and evolves to macules, vesicles, pustules, and crusting. The lesions are firm, well circumscribed, umbilicated or confluent and can be in different states of the disease in different parts of the body (3,10-12) (Figure 2). The rash can solve scarring tissue. The lesions have been found also in the mouth, the nose, and the anus as the starting point of the disease. In these cases, the main symptoms are anal pain and rectal bleeding (8). Lymphadenopathy is an important sign in the monkeypox infection. In immunocompromised patients the disease tends to have a more severe presentation with a higher mortality rate compared to the rest of groups. These masses can be presented in the neck, the armpit and the groin, uni or bilateral. (9-11)

FIGURE 2. *Natural history*



Given the nature of the lesions, confusion with other dermatological conditions may be facilitated during pregnancy. The presentation of urticarial papules and plaques, as well as other sexually transmitted infections such as herpes, syphilis, lymphogranuloma venereum, varicella zoster, molluscum contagiosum and chancroid can overlook the possibility of early detection of Monkeypox associated lesions. Given clinical suspicion, it is essential to carry out diagnostic tests, especially in the presence of risk factors (9,12,13).

Transmission

Every patient with suspicious lesions must be considered as contagious when the symptoms start, during the prodromal state and, above all, during the active period of the rash (12,14). The virus transmission, as a cardinal characteristic of every zoonosis, occurs because of the bite or scratch from an infected animal, but also because of the contact with fluid coming from active lesions. It has also been described the sexual intercourse as a source of transmission. Most of the initial cases presented with ano-genital lesions, lesions in the mouth and proctitis, without a previous prodromal phase and with the common association of sexual intercourse among men (3,11,15). The children are more susceptible to present with the most severe forms of the disease (11). With the objective of minimizing the transmission, every symptomatic patient must be isolated immediately, with the posterior covering of every lesion, independent of the staging, to avoid the contact with the skin and mucous membranes from healthy people, as well as the promotion of the high efficiency mask face (3,14). Patients must avoid sexual intercourse, exchange of personal elements and sex toys (13,14). Every patient is considered as infectious until every lesion has been solved, the crusting has fallen and the scar appears (12,13). There are no studies that have confirmed the vertical transmission of the virus. Nevertheless, it is recommended that special care must be taken at the moment of labor, in which no lesions must be present in the perineal region. In case of having perineal lesions, the cesarean section surgery must be considered, with the appropriate protection for the mother, the fetus and the health services (16). Similarly, to the dynamics presented by the Johns Hopkins Hospital, the CDC launched a website that allows a permanent update of the global number of cases: https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html

Approach in the obstetric patient with suspicion of Monkeypox infection

As a general principle, the screening in asymptomatic patients is not recommended. If there is suspicion of infection, a complete clinical history must be made with emphasis in traveling history to endemic zones, contact with people with lesions, or contact with people with confirmed diagnosis (12), along with a complete physical exam that must be systematic, including the visual inspection of the mucous membranes in the mouth, nose and perineal region. The active search of lymphadenopathies is mandatory (3,12). All patients with fever, rash and lymphadenopathies must be isolated immediately in an individual room. Likewise, the obstetrician in charge of the case must have all the high efficiency personal protection elements, so the risk of transmission can be diminished. In view of the necessity of the airway management, any procedure must be taken in a well-ventilated room. The individualized and controlled cleaning of clothing and items in contact with the patient must be managed by highly trained personnel (3,17).

The diagnosis of the infection is based on a two-step standard that is based on the detection of the orthopoxvirus. Multiple samples from different lesions at different stages of infection should be taken to ensure an adequate sample for the laboratory and to decrease the chance of a false-negative result. The diagnostic test of choice is the specific Polymerase Chain Reaction (PCR) (3,15,18). The sensitivity of specific PCR for virus detection in amniotic fluid is unknown. By analogy with other DNA viruses, it is likely to be detectable in amniotic fluid once significant urine is produced by the fetal kidneys, i.e., by 18

weeks' gestation (15). Once the diagnosis is confirmed, a multidisciplinary team must be formed that includes specialists in Maternal-Fetal Medicine, Infectious Diseases and Neonatology (19).

Of the 7 cases reported in the literature, 5 pregnancies had an adverse fetal outcome: three spontaneous abortions and two stillbirths. The histopathological study revealed the presence of maculopapular lesions, hepatomegaly, ascites and fetal hydrops. The presence of the virus in the fetuses studied was determined by specific PCR, with high viral loads. Of the remaining two reported cases, one ended in eutocic vaginal delivery with a healthy newborn with no evidence of lesions suggestive of contact with the virus, while the last case ended in preterm delivery 6 weeks after the onset of symptoms with signs symptoms suggestive of congenital monkeypox infection (5-7,15,20,21). Based on conjecture derived from smallpox and monkeypox infection in these cases, it is unclear whether the infection is more severe in pregnancy or whether the risk of infection increases with pregnancy. Reported cases of smallpox in pregnancy had a high fatality rate and increased risk of postpartum obstetric hemorrhage. The extrapolation of perinatal outcomes in patients with smallpox can be a starting point to understand the expected effects in cases of infection by other orthopoxviruses. Preterm birth, spontaneous abortion, fetal death and vertical transmission have been reported in multiple cases of common smallpox, however the behavior of monkeypox and its association with maternal and perinatal outcomes is still unknown (3,19,22)

Case definitions of public health interest

The case definition in pregnant patients carried out by the FIMMF takes into account the guidelines given by the WHO and the CDC (23,24):

- **Suspicious case in pregnant women:**
  - New characteristic rash or the presence of one of the following:
    - Pregnant women who present with acute rash since January 1st, 2022. This rash has not a clear explanation.
    - One or more of the following signs or symptoms: headache, acute fever, lymphadenopathy, muscle ache, backache, asthenia
- **Probable case in pregnant women:**
  - *Orthopoxvirus DNA* by PCR in a clinical sample **or**
  - *Orthopoxvirus* DNA using immunohistochemistry or electronic microscopy or
  - Demonstration of detectable levels of IgM antibodies from 4 to 56 days after the rash started.
  - Pregnant women that fill the definition of suspicious case and one of the following:
    - Epidemiological nexus or
    - A probable case or a confirmed one from the previous 21 days, with multiple sex partners
- **Confirmed case in pregnant women:**
  - Demonstration of viral DNA from monkeypox by last generation PCR sequencing in a clinical sample or
  - Isolate the Virus of monkeypox culture from a clinic sample
- **Discarded case in pregnant women:**
  - Suspicious or probable case for which the laboratory testing from skin lesions, with negative PCR sequencing for monkeypox virus.
- **Definition of contact in pregnant women:**
  - Prolonged contact face to face, included health workers without personal protection equipment (Gloves, coat, ocular protection, face mask).
  - Direct physical contact with skin or mucous membranes lesions, including sexual intercourse, or contact with contaminated materials like clothes and personal use objects

- **Epidemiological criteria**
  - Within the first 21 days after the beginning of the disease:
  - Contact with a person with skin rash with confirmed or probable diagnosis of monkeypox or
  - Recent trip to a monkeypox endemic country or
  - Contact with a death or live animal with high suspicion of having the virus
- **Exclusion Criteria**
  - A case can be excluded as suspicious, probable or confirmed if:
  - There is an alternative diagnosis that fully explains the disease or
  - A person with symptoms consistent with monkeypox without rash 5 days after of the onset of the disease

Severity of infection: inpatient and outpatient management.

Within the general approach to obstetric patients, it is necessary to determine the place of care, isolation and follow-up of this group. It is for this reason that we consider that it is necessary to have clear guidelines that allow the adequate management of patients with suspected or confirmed monkeypox diagnosis.

We consider the population to be at very high risk, based on the probability of generating complications, the immunosuppressed patients and pregnant patients. However, beyond paying special attention to this population, it is important to define the severity criteria that should be actively sought in all patients with suspected infection. Thus, the first severity criterion to take into account is skin rash. The number of lesions, regardless of the stage of the lesion, implies a better or worse prognosis and is related to the probability of complications, especially in the pregnant woman and in the fetus. Cases with 5 to 25 lesions are considered mild, moderate with 26 to 100 lesions, severe with 101 to 250 lesions, and very severe with more than 250 lesions. Similarly, and following the line of clinical examination, constitutional symptoms are part of the evaluation of the prognosis of the disease. We consider fever, its degree (temperature greater than 38°C) and its duration (7 days or more) as a fundamental factor in the initial evaluation; the presence of cervical lymphadenopathies, regardless of the number, consistency or location; dysphagia and pain in the oral cavity; and the presence of hypoxemia defined as oxygen saturation less than 95% in room air at sea level (25,26). It is recommended that patients presenting with these symptoms should be hospitalized regardless of the trimester of pregnancy.

The indications for hospital admission for management and surveillance are listed below (27):

1. Pneumonia, with or without respiratory distress
2. Encephalitis or meningitis
3. Eye injuries with risk of vision loss, as well as eye pain or visual disturbance
4. Pharyngeal lesions that prevent swallowing of liquids or compromise the airway
5. Severe cellulitis with organic compromise
6. Persistent fever in patients with immunosuppression
7. Proctitis requiring IV analgesia and/or gastrointestinal rest
8. Dehydration
9. Persistent vomiting or diarrhea
10. Sepsis

On the other hand, patients with a mild or moderate spectrum of the disease do not require in-hospital management. This group of patients can be isolated at home for the duration of the infection. This isolation must have the necessary measures to avoid contact with the rest of the inhabitants of the house. The handling of clothing, toiletries, and personal items must be careful and require special handling. Symptoms can be managed with antipyretics and analgesics, as well as oral rehydration salts in case of persistent emesis or liquid stools. It is necessary to give advice to patients and their relatives about the warning signs to take

into account and for which they should consult the emergency service. The use of empiric antibiotics for the management of skin lesions is not recommended. In case of superinfection of the lesions, the use of antibiotics aimed at covering gram-positive germs is recommended (26).

In 2003, a study was carried out that sought to define the severity criteria in patients with monkeypox, during the epidemic outbreak that occurred in the United States that same year. With a cohort of 34 patients with a confirmed diagnosis of infection, it was found that almost 100% of the patients had a skin rash, followed in frequency by the presence of fever, chills, lymphadenopathy, headache, sore throat, myalgia, and cough. The spectrum of symptoms was much greater, but the frequency of appearance was lower compared to the first symptoms. 56% of the cases presented infection after contact with animals. 24% of the patients reported having underlying conditions such as Hepatitis, Asthma, Hydrocephaly, pregnancy, lupus nephritis, hemophilia and bone marrow transplant. No significant differences were found between the samples taken at the beginning or at the end of the clinical course. Half of the patients presented elevated transaminases, hyperuricemia, hypoalbuminemia, leukocytosis, and thrombocytopenia. 5 patients were classified as severely ill and 9 patients required hospitalization. Among the complications reported for the entire cohort, a retropharyngeal abscess was found that required advanced management of the airway, bacterial superinfection with an unknown germ, and corneal ulcer. None of the hospitalized patients died during follow-up. Pediatric patients presented a higher frequency of admission to the ICU, although the progression of the severity of the disease was similar to that of the adult population (25).

IFMFM approach to monkeypox infection in pregnant women according to the trimester

We consider that, given the cases reported in the literature and pregnancy being a state of dynamic changes, it is important to differentiate contact with the virus and its implications depending on gestational age. Thus, in this guide we make a distinction between the management and follow-up of patients according to the trimester in which the infection occurs.

During the first trimester, and based on the cases reported in the literature, there is an increased risk of spontaneous abortion. Therefore, all patients with suspected infection during the first trimester should receive counseling about symptoms such as: pelvic pain, genital bleeding, persistent emesis, in addition to the alarm symptoms of monkeypox infection.

Once the pregnancy enters into the second trimester, and more specifically the second half of pregnancy, the risk of miscarriage is modified by the risk of preterm birth. It is for this reason that all patients with monkeypox infection in the second trimester must have a mandatory screening cervicometry between weeks 20 and 24, with the aim of identifying the risk of preterm birth early. Additionally, the assessment of fetal well-being is based on obstetric ultrasound, with special attention to estimated fetal weight, amniotic fluid volume, and the presence of ultrasound signs of perinatal infection. It is recommended to place special emphasis on fetal growth patterns and placental function parameters, for which we recommend performing fetoplacental Doppler after resolution of the infection, according to the severity of the infection.

Moving into the third trimester, the risk of preterm labor does not go away; however, another extrapolated risk is added from the cases reported in the literature, such as intrauterine fetal death. The risk of fetal death should be an essential point in the counseling of patients with monkeypox infection, especially in severe cases. Therefore, it is necessary to alert and educate in the perception of fetal movements, their recognition pattern and behavioral fetal states. Likewise, it is recommended that all patients during the third trimester have a weekly evaluation together with a biophysical profile with fetoplacental Doppler, to detect early placental causes that may lead to fetal death in utero. It is recommended that during the infection at the end of pregnancy, after week 37, if fetal well-being is found without signs of alteration in

placental function, the delivery should be deferred until the time of resolution of the infection. Termination of pregnancy is considered mandatory in the event of severe maternal systemic compromise, risk to maternal health, or unsatisfactory fetal status

Sampling

Any patient who meets the probable case definition should collect the following samples:

1. Vesicle exudate
2. Smear of skin lesions and scraping or picking of scabs
3. Pharyngeal swab
4. Serum

Sampling in asymptomatic patients is not recommended. Samples should be collected at the time of rash onset. It is FIMMF recommendation to take samples from lesions in different stages. Crusts and exudative from lesions should be collected in separate tubes.

The procedure for collecting samples from skin lesions is described below:

- Choose a lesion that has an evolution time less than 10 days
- Apply saline under pressure
- In case of presenting with vesicles:
  - Lift the skin of the vesicle with a lancet
  - Rub the base of the lesion with a sterile swab without causing bleeding
  - Place the swab in a dry sterile plastic tube
  - Repeat the same process in other vesicles

If scabs are found, these should be scraped off and taken with a scalpel blade. The samples must be stored in different tubes. It is recommended to wash the affected area with soap and water after taking the sample. All samples must be kept at a temperature of -20°C and must be sent immediately to the nearest public health laboratory (28).

In case of suspecting a differential diagnosis suggestive of sexually transmitted infection, the following samples should be taken (27):

1. PCR for N. gonorrhoeae, C. trachomatis, M. genitalium in urethra, vagina, rectum, and pharynx.
2. Serology for HIV, syphilis, HCV, HBV
3. Herpes Simplex Virus type I and II

It is recommended that vaccination data be collected from all patients with suspected monkeypox infection or suspected sexually transmitted infection (27).

Treatment and vaccination

Similarly, to the natural history of most viruses, the treatment of monkeypox is based on the symptomatic management of the patient and the control of complications associated with the appearance of lesions on the skin and mucous membranes, as well as the management of pain in the genital and anal region. It should be noted that the pregnant population is in a group of patients with high susceptibility of complications, especially of the infectious type. Regardless of the trimester in which the infection occurs, or whether the infection is acquired or active during the breastfeeding period, the risk of complications represents a concern and a management objective in any obstetric care unit (3,29).

Among the support measures recommended during pregnancy we can find the following (27):

General measures in pregnant patients:

- Thromboprophylaxis with low molecular weight heparin (LMWH), with dose adjusted by weight.
- Intravenous fluids in case of oral intolerance or hemodynamic instability. It is also recommended in case of extensive skin involvement.
- Prophylaxis for stress ulcers
- Laxatives in cases of proctitis
- Management of skin lesions
- Management and monitoring of eye injuries

- Supplemental oxygen or non-invasive mechanical ventilation if necessary

Medications recommended in pregnancy:

- Paracetamol for fever management (500 mg to 1 gram every 6 to 8 hours)
- Ibuprofen in case of pain (400 mg every 8 hours). Caution is recommended in pregnancies greater than 32 weeks due to the risk of closure of the ductus arteriosus.
- Tramadol in case of pain (50 to 100 mg every 4 to 6 hours)
- Loratadine (10 mg every 24 hours) or Hydroxyzine (25 mg every 24 hours) in case of intense itching.
- In case of bacterial superinfection, the use of:
  - Oral cephalexin 500 mg every 6 hours for 5 days.
  - Oral clindamycin 300 to 600 mg every 6 to 8 hours for 7 days
  - Trimethoprim/sulfamethoxazole is not recommended for the management of skin lesions during pregnancy.

General measures for the management of skin lesions in pregnancy:

- Short nails to avoid scratching
- Hand washing
- Clean and dry lesions. It is recommended to wash the lesions 2 to 3 times a day.
- Use of topical antiseptic
- Consider keeping exuding lesions covered
- In case of ulcerative genital lesions, the use of sitz baths is recommended and topical anesthetics.
- In case of oral lesions, the use of mouthwashes with 1% lidocaine is recommended.
- In case of superinfection, the use of systemic oral antibiotics is recommended.
- Crusty lesions can be managed with a thin layer of petroleum jelly.

General measures for the management of eye injuries in pregnancy:

- In case of eyelid injuries, the use of patches is recommended given the difficulty in opening the eye
- Constant hand washing is recommended as well as avoiding contact of the hands with the eyes
- The use of contact lenses should be avoided
- Tobramycin or Azithromycin in eye drops or gel can also be used
- Priority assessment by Ophthalmology is recommended to define the need for ocular antivirals

General measures for the management of proctitis in pregnancy:

Proctitis is defined as inflammation of the rectal mucosa that can cause tenesmus, fecal urgency, hematochezia, and anal pain. In case of extension of the condition, proctocolitis may occur with the presence of pain, abdominal distension and meteorism. This clinical presentation is more frequent in patients who have anal intercourse. It is recommended as general measures:

- Oral anti-inflammatories (see section "Recommended medications in pregnancy")
- Topical or systemic corticosteroids (avoid systemic glucocorticoids due to their effect on the fetus)
- Topical or oral antibiotics (avoid groups of antibiotics such as quinolones, fluoroquinolones, and tetracyclines)
- Evaluation by General Surgery in case of complications.

To date, there is no approved and/or specific antiviral treatment for the management of monkeypox infection. However, it is proposed to apply two antivirals and a vaccine with immunoglobulin to prevent the spread of the virus, reducing infectiousness (28). Tecovirimat, an antiviral approved by the FDA (Food and Drug Administration), is available in oral and intravenous presentations. Both presentation forms have

been used in the current outbreak within the United States. However, there are still no studies evaluating the effect on the mother or fetus during pregnancy or lactation. Studies in mice did not show teratogenic effects using doses 23 times higher than the toxic dose (11,28). Patients with high priority for administration of Tecovirimat are considered to be those with pneumonia, encephalitis or meningoencephalitis, corneal ulcers, risk of vision loss, pharyngeal lesions that prevent fluid intake and total or partial compromise of the airway (27).

Cidofovir, the other antiviral used during the current outbreak, has been used in the management of patients with Cytomegalovirus infection and HIV coinfection. This drug has also been used in animal models and has been associated with embryotoxicity and teratogenicity. The FDA has classified it as category C, which is why it is not recommended for the management of infection in pregnant patients. These management options should be considered only in severely ill patients or those at high risk of complications (3,16,20) (Table 1).

TABLE 1. ANTIVIRAL TREATMENT

Antiviral	Tecovirimat	Cidofovir
Administration	Oral	Intravenous
Dosage	13-25 Kg: 200 mg/12h 26-40 Kg: 400 mg/12h >40 Kg: 600 mg/12h	5 mg/kg weekly only dose
Presentation	Capsule 200 mg Vial 200 mg/20 mL	Vial 75 mg/mL
Duration	14 days	Two to four weeks
Precautions	Blood count, renal and liver function control	Blood count, renal and liver function control
Contraindications	None	Pregnancy CrCl < 55 cc/min Cr > 1.5 mg/dL Urine protein > 100 mg/dL Nephrotoxic drugs

Adapted from: Ministerio de Sanidad, España. DOCUMENTO DE CONSENSO SOBRE MANEJO DE LA VIRUELA DEL MONO EN PACIENTES HOSPITALIZADOS [Internet]. 2022. Disponible en: https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/alertaMonkeypox/guiaDeManejo.htm

The application of Hyperimmune Intravenous Immunoglobulin (IV IG) has been authorized by the FDA for the treatment of Orthopoxvirus infections. There are currently no studies in humans or animals during pregnancy. However, other immunoglobulins have been widely used in pregnancy without adverse effects. The FDA has classified it as category C due to the lack of information from well-designed studies (3,20).

Various studies have shown that smallpox vaccination provides cross-protection against other Orthopoxvirus species, including Monkeypox. About 90% of current cases do not have such protection since they were born after the cessation of vaccination following the global smallpox eradication program. (7). There are currently two smallpox vaccines, JYNNEOS (IMVANEX) and ACAM2000, authorized and recommended by the FDA and the European Medicines Agency (EMA), which have been shown to prevent the disease in patients at high risk of infection (30)

JYNNEOS is a non-replicating live attenuated virus vaccine, with insufficient data from its use in pregnant women to determine associated risks. However, animal studies have shown no evidence of harm to the developing fetus. The safety and efficacy of JYNNEOS during lactation have also not been evaluated and its excretion in breast milk is unclear. However, as this is a replication-deficient vaccine, it should not pose a risk to infants. (31).

According to the CDC recommendation, JYNNEOS can be offered as the vaccine of choice for pregnant or lactating women, as this population is at high risk, (CDC Pregnant) after substantial exposure to the virus, evaluating the risk of infection for the mother and the fetus vs the benefits of vaccination in consultation with the treating physician so that an informed and shared decision can be made. (15) Additionally, there are data available on its use in at least 300 pregnant women in whom no increase in adverse pregnancy outcomes was observed (32).

In contrast, the ACAM2000 vaccine is a replicating viral vaccine, which is available under an investigational new drug application, contraindicated in pregnancy and lactation, due to its association with pregnancy loss, risk of birth defects and the current availability of the vaccine. non-replicating vaccine. (30,31)

Currently both the Center for Disease Control and Prevention (CDC) in the United States and the United Kingdom Health Security Agency (UKHSA) recommend vaccination in (32,33):

- Health workers starting to care for a patient with confirmed monkeypox and staff evaluating suspected cases.
- Persons who have had close contact with a patient with confirmed monkeypox infection. (GOV UK – NYC Health)
- People with conditions that increase the risk of serious illness, such as immunosuppression or another entity that weakens the immune system such as pregnancy.

It is recommended to start the scheme in the first 4 days after contact and up to 14 days and the application of the second dose should be carried out 4 weeks after the first (33,34). With the use of JYNNEOS, and given the lack of sufficient studies, it is presumed that the immune response takes 14 days to establish after the application of the second dose. (31)

The smallpox vaccine could attenuate the potential for viral replication. The first- and second-generation vaccines contain live attenuated viruses with replication potential. However, third-generation vaccines, which use non-replicating viruses, present an alternative to the management of pregnant patients. This generation of vaccines received a distribution license in 2019, which prevents having sufficient data to define its safe use in pregnancy. Vaccination data for smallpox in pregnancy are based on data from first- and second-generation vaccines. Current data have found no association between vaccination for smallpox and spontaneous abortion (RR 1.03 CI95% 0.76-1.41) or congenital defects (RR 1.25 CI95% 0.99-1.56) (18). There is currently no vaccine approved for use during pregnancy. Since the available vaccines for smallpox are non-replicating, there is no theoretical reason for concern about their use in pregnancy. Animal studies have reported no adverse fetal effects (16).

Patients´ transportation

If transportation is required, the health personnel in charge of transportation must wear high-efficiency personal protection elements (gloves, N95 masks, protective sleeves, goggles). The care center that will receive the patient must be informed so that they can prepare the facilities and trained personnel to manage the condition. The patient should always use personal protection elements, and in case of active lesions, they should be covered with long sleeves. The ambulance where the patient will be transferred must be properly cleaned once the transfer is complete, so that it can be used by another patient if required. Any surface that has come into contact with the patient must be cleaned with a 1% hypochlorite solution or its equivalent. All disposable material used during the transfer process must be placed in red biohazard bags (35)

Prevention

Primary prevention of monkeypox infection involves immediate isolation of highly suspected or confirmed infected individuals. Isolation includes avoiding contact with other humans and animals, avoiding sexual contact, and post-exposure vaccination. The follow-up of these patients during the incubation period, the period of infectiousness, resolution of lesions and symptoms is mandatory. The minimum isolation time is 21 days. Close contacts who remain asymptomatic can continue their routine activities (12,36)

Contact with the newborn and breastfeeding

The benefit of skin-to-skin contact and early breastfeeding in reducing adverse neonatal outcomes in the early neonatal period is well known. However, given the risk of neonatal monkeypox, children of mothers with active lesions should not be exposed to skin-to-skin contact or initiate early breastfeeding. The best way to reduce the risk of mother-to-child transmission is immediate isolation of the mother. Counseling about the risk of neonatal infection should be offered. If the

patient insists on early contact with the newborn, special precautions should be taken, including avoiding skin-to-skin contact, wearing clothing that covers all the patient's skin from neck to toe, the use of gloves and the use of high-efficiency face masks. These measures should not be interrupted until the patient enters the phase of resolution of the lesions. The isolation, the lack of contact with the newborn, and the anxiety generated by the infection should suggest the need for evaluation by the Mental Health Unit (31).

Post exposure prophylaxis

Post-exposure prophylaxis is aimed at reducing the risk of infection progression once in contact with patients with a confirmed diagnosis. The vaccine prevents infection if given within the first 4 days after contact. If the vaccine is applied between 4 and 14 days after exposure, the expected effect is a reduction in symptoms but not prevention of the disease (37).

Pre-exposure prophylaxis

Live attenuated non-replicating virus vaccine is available for pre-exposure prophylaxis for prevention of monkeypox and smallpox infection. This vaccination is reserved for patients with risk factors such as health personnel in contact with suspected patients. Pregnancy is not considered a contraindication to receiving pre-exposure prophylaxis. Animal studies have shown no teratogenic effects on developing fetuses (38).

CONCLUSIONS

Pregnant or recently pregnant women with uncomplicated or mild monkeypox may not require acute hospital care, but outpatient management with close follow-up may be preferred; those with severe or complicated disease should be admitted on an inpatient basis for care, as they require optimized supportive care or interventions to improve maternal and fetal survival (Figure 3).

Pregnant and recently pregnant women with monkeypox should have access to specialist, respectful, and woman-centered care, including obstetrics, gynecology, maternal-fetal medicine, and neonatal care, as well as mental health and psychosocial support, with provision for to treat maternal and neonatal complications. The mode of delivery should be individualized, based on the obstetric indications and the woman's preferences. It is recommended that induction of labor and cesarean section be performed only when medically justified and based on maternal and fetal status. Pregnant and recently pregnant women who have recovered from monkeypox should be enabled and encouraged to receive routine prenatal, postpartum or abortion care, as appropriate. Additional care should be provided if there are any complications.

Table 2 and 3 summarizes the recommendations that should be considered during pregnancy in relation to infection and risks of monkeypox.

TABLE 2. SUMMARY OF RECOMMENDATIONS

	Recommendations in Pregnant Patients–Maternal-Fetal Medicine–International Foundation for Maternal-Fetal Medicine
1	It is recommended to maintain a high suspicion of monkeypox infection in patients with risk factors or who have traveled to endemic areas.
2	It is recommended to start the monkeypox infection protocol in all patients who present with fever, mucocutaneous rash and lymphadenopathy of any location.
3	It is recommended to isolate all patients with a high suspicion of monkeypox infection until active infection has been ruled out or until 21 days of isolation have been completed. Isolating asymptomatic contacts is not recommended.
4	Universal screening of asymptomatic patients is not recommended in order to reduce the transmissibility of the virus.
5	The use of specific PCR for monkeypox is recommended as a confirmatory diagnostic test for infection.
6	Counseling the patient regarding the potential adverse effects associated with monkeypox infection, such as spontaneous abortion, preterm delivery, and stillbirth, is recommended.
7	The use of Tecovirimat and intravenous immunoglobulin is recommended for the management of cases of severe monkeypox infection. The use of Cidofovir is not recommended due to its association with embryotoxicity and teratogenicity in animal models.
8	It is recommended to hospitalize all pregnant patients with suspected monkeypox infection with signs and symptoms of severe infection: more than 100 lesions, persistent fever, lymphadenopathy, hypoxemia.

9	Outpatient management and follow-up is recommended for all patients with mild or moderate signs and symptoms of monkeypox infection.
10	It is recommended to transport patients with suspected monkeypox infection according to the guidelines for biosafety measures, use of highly efficient personal protection methods and cleanliness of areas in contact with patients.
11	The use of caesarean section as a routine route of delivery in patients with active monkeypox infection is not recommended. The route of delivery must be defined based on obstetric factors exclusively.
12	It is recommended to form a multidisciplinary team made up of specialists in Maternal-Fetal Medicine, Infectious Diseases, Psychiatry, Critical Care, Ophthalmology and Neonatology.
13	It is recommended that the best test for fetal well-being assessment is based on the gestational age, the stage of the infection and the general condition of the patient.
14	Skin-to-skin contact is not recommended, as is early breastfeeding in patients with active lesions.
15	Requesting an assessment by the Mental Health Unit is recommended for all pregnant patients with a confirmed or suspected diagnosis of monkeypox.
16	Pre- and post-exposure prophylaxis is recommended for all patients who have had close contact with confirmed cases.

TABLE 3. IFMFM CHECKLIST FOR PREGNANT PATIENTS WITH SUSPECTED MONKEYPOX INFECTION.

Vital signs and pain	Temperature, heart rate, blood pressure, respiratory rate, oxygen saturation, level of consciousness, visual analog scale, blood glucose, BMI.
General condition	1. Is the patient able to eat and drink without support? 2. Does the patient sit and walk independently? 3. Has the patient lost weight since the onset of symptoms?
Rash	Lesion staging: macules, papules, vesicles, pustules, exfoliation Location: face, arms, chest, abdomen, genitals, legs, mucous membranes Number of injuries: • Mild: 5 -25 lesions • Moderate: 26 – 100 lesions • Serious: 101 – 250 lesions • Very serious: >250 lesions Exfoliation percentage (severity >10%)
Secondary bacterial infection	Cellulitis, abscesses, pyomyositis, necrotizing soft tissue infection
Neurological state	Seizures, coma.
Hydration	Skin turgor, urine output, incomes and outputs, thirst.
Perfusion	Capillary refill, heart rate Urinary output (>0.5 cc/Kg/hour) Skin mottling
Breathing	Respiratory rate, arterial oxygen saturation, signs of respiratory distress
Nutritional state	Changes in appetite, weight loss, BMI
Obstetric assessment	Genital bleeding, uterine contractions, cervical changes.
Laboratory	Sodium, Potassium, Chlorine, BUN, Creatinine, AST/ALT, Glucose, Blood count, Coagulation times, calcium, albumin.
Fetal wellbeing tests and cervical assessment	First Trimester: Transvaginal Obstetric Ultrasound Second trimester: Transabdominal obstetric ultrasound, cervicometry Third trimester: biophysical profile, obstetric ultrasound, fetoplacental Doppler, fetal monitoring, fetal movements, cervicometry.

Adapted from: World Health Organization. CLINICAL MANAGEMENT AND INFECTION PREVENTION AND CONTROL FOR MONKEYPOX. WHO/MPX/Clinical_and_IPC/20221. junio de 2022

DISCLOSURES

All the authors and the members committee, together with the guideline development group, have filled out the conflict of interest declaration format, detailing the personal, professional or business interests that may be perceived as real or potential with respect to this guideline publication. Any conflict of interest has been resolved through an approval process by the membership committee. The Maternal-Fetal Medicine Foundation (FIMMF) has not accepted or solicited any commercial involvement in the development of the content of this publication.

This document has been submitted for internal peer review through a multi-level committee within the FIMMF. This revision includes critical feedback from the Publications Committee and has received final approval from the FIMMF Executive Committee. The FIMMF accepts full responsibility for the content of the current document. The publications made by the FIMMF are not reviewed by the editorial committee of any national or international academic society. As a plan for improvement, the FIMMF reviews its publications every 24 to 36 months, and determines the need to update its documents. Additional details regarding publications made by the FIMMF can be found at www.mmfetal.com

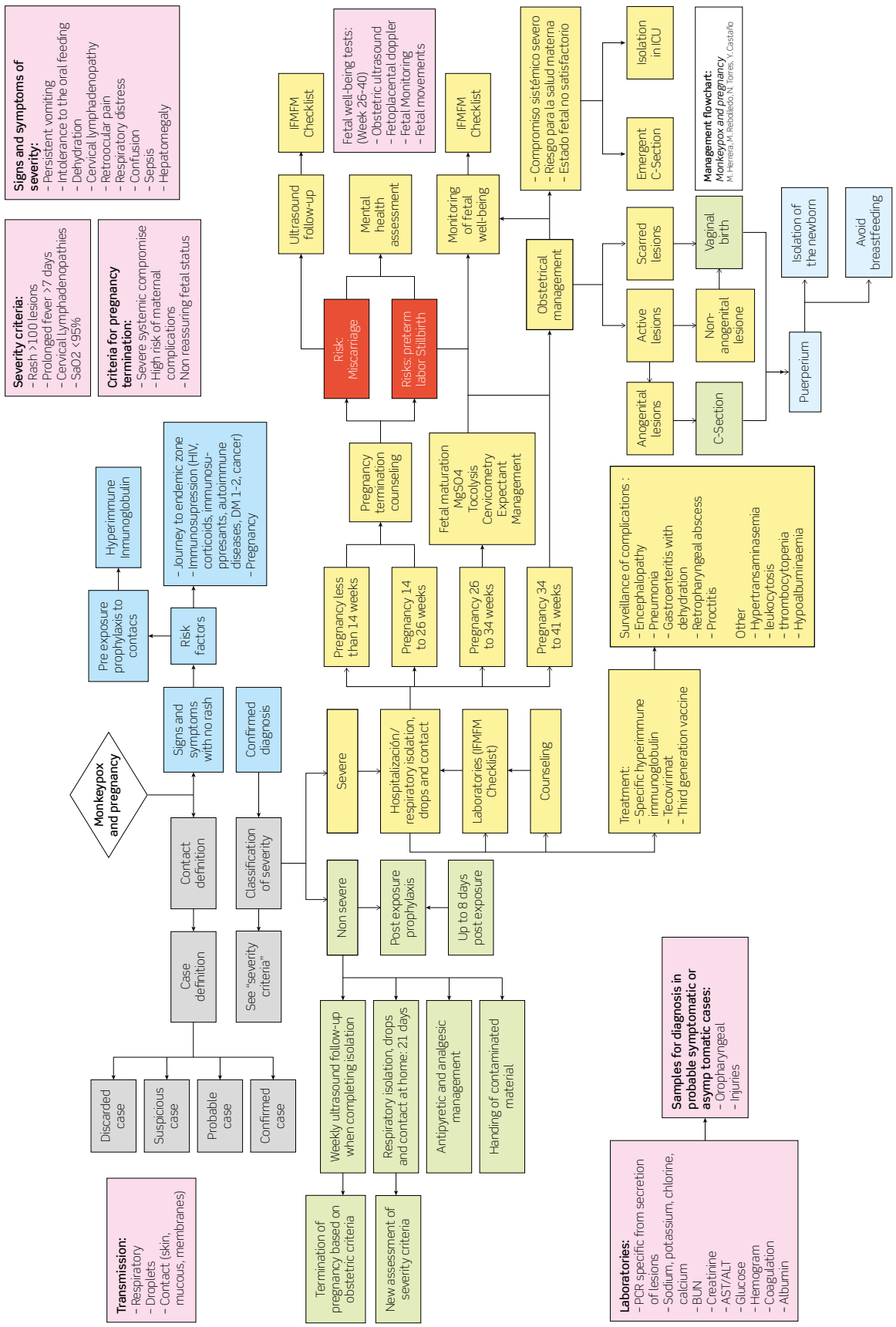


FIGURE 3. Flowchart for healthcare in pregnancy for monkeypox

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