Congenital herpes virus infections

Infecções congênitas por herpes-vírus

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ABSTRACT

Congenital infections by the herpes virus show high prevalence or are responsible for high morbidity and mortality in newborns. In this review, the herpes virus simplex, Varicella zoster virus, and Cytomegalovirus are addressed as infectious agents in pregnant women, fetus, and newborns, and include measures for the prevention of mother-to-child transmission and recommendations for the propaedeutics and therapy of both mother and child.

Key words: Herpes Simplex; Herpes Zoster; Cytomegalovirus; Infectious Disease Transmission, Vertical.

INTRODUCTION

During pregnancy, woman can be exposed to numerous infectious agents (viruses, bacteria, protozoa, and fungi) that affect the fetus and can be a major cause of perinatal morbidity and mortality. The child can be infected during intrauterine life (congenital infections), childbirth or the first weeks of life (perinatal infections).1

The most frequent congenital infections are toxoplasmosis, syphilis, acquired immunodeficiency virus, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV). Viruses are often involved in congenital infections and the most pathogenic group for man belongs to the family of the herpes viruses. Based on national publications, the estimation of the incidence of some congenital/perinatal infections in Brazil (infected/live births, such as cytomegalovirus (26/1000)2 and herpes simplex (1/5000)3 are possible.

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METHODS

This was a review study in which the search on the medical literature databases (National Library of Medicine-PubMed-MEDLINE; Latin American literature and Caribbean Center on health sciences-LILACS; Scientific Electronic Library Online-SCIELO) was conducted in addition to in health reference institutions (Center for Diseases Control and Prevention and the Food and Drug Administration). The following descriptors were used: herpes simplex; herpes zoster; chickenpox, cytomegalovirus; vertical transmission of infectious disease.

APPROACH TO THE MAJOR CONGENITAL INFECTIONS BY THE HERPES-VIRUS, HERPES SIMPLEX VIRUS (HSV), HERPES VIRUS 1 AND 2

Although rare and with a prevalence of around 1% transmission, congenital infection by the herpes simplex virus leads to high morbidity and mortality in newborns. The manifestations may be mucocutaneous, neurological, or disseminated (Figure 1). The disseminated forms occur in 50% of cases and present 30% mortality. When there is involvement of the nervous system, in the isolated or disseminated forms, there is the likelihood of neurological abnormalities or sequelae in more than 70% of the involved children. Infection can occur in primary forms but also in recurrent forms with less frequency. The correlation between some strains and transmission occurs primarily involving the type II virus, however, the type I infection involvement in acute forms have already been reported. The transmission is also related to viral shedding in the genital tract.

Via labor

The cesarean delivery is indicated for patients with clinical manifestations and active or prodromes at the time of delivery although it does not completely eliminate the risk of transmission and must be carried out, preferably as the elective form if there is disruption of membranes in less than four hours. There are authors who recommend performing caesarean if the primary infection occurred in the last four to six weeks of gestation due to viral replication and production of insufficient antibodies for the protection of the newborn.

Diagnosis

All pregnant woman or parturient should be investigated on history of prior illness, and physical examination should be performed to detect active lesions.
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Treatment

Pregnant Woman

The first episode of infection in pregnant women must be specially treated in the third trimester of pregnancy and when there is evolution towards vaginal childbirth due to high rates of mother-to-child transmission, around 50\%.\(^5,10,12\) The therapeutic and prophylactic schemes cited in the literature\(^4,10-14\) are presented in Table 2.

Although they are not drugs of choice during pregnancy, the experience has not demonstrated fetal or neonatal adverse events, with the greatest experience being with acyclovir. However, during breastfeeding, only acyclovir and valacyclovir are described as safe. Patients with disseminated herpes should use intravenous medication, or intravenous therapy may be used (10 mg/kg/dose at every 8 hours) for two to seven days, with maintenance of oral treatment until completing 10 days. Recurrent episodes can also be treated with schemes of five days.\(^5,7,9\)

Currently, the Center for Diseases Control and Prevention\(^11\) recommends serology in symptomatic patients although it is not recommended by the Brazilian guidelines. The history and guidelines are crucial for the conduct and prevention and some authors advice on serological testing for triage and virological and molecular tests for diagnosing.\(^10\) Pregnant women with a diagnosis of the first episode in the first trimester of pregnancy can be traced with cultures, molecular tests, or antigen research to identify viral replication, which contributes to the decision on type of delivery.\(^10\) Serology for HSV 1 and 2 can also be requested for the parturient if available in the maternity ward.\(^12\)

Despite viral culture being the most sensitive method, the polymerase chain reaction (PCR) technique is indicated for the diagnosis in specimens from newborns, especially in liquor and blood. Surface material such as the conjunctiva, oral mucosa, nasopharynx, rectum, and cutaneous lesions can also be obtained.\(^11,12\) The exposed newborn must be observed for 7 to 14 days, which refers to the incubation period of the virus. The diagnostic conduct for the newborn can be stratified according to the symptomatology and propedectics results presented in Table 1.\(^3,5,9,12-14\)

<table>
<thead>
<tr>
<th>Table 1 - Propedectics with newborn exposed vertically to herpes simplex</th>
</tr>
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<tbody>
<tr>
<td>Investigation</td>
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</table>
| - if asymptomatic at 24 hours of life | a) research for HSV DNA by polymerase chain reaction in surface material (conjunctiva, oral mucosa, nasopharynx, and rectum) and blood.  
  b) paired serology (IgM and IgG) with mother, for HSV type 1 and 2. |
| - if evolving with signs and symptoms at any moment | a) Investigation of target organ:  
  - hemogram;  
  - hepatic function;  
  - routine liquor;  
  - electroencephalogram and brain computed tomography (if CNS is involved);  
  b) etiologic investigation:  
  - polymerase chain reaction for HSV DNA in liquor  
    (and material from skin lesions and other specimen, if present). |

<table>
<thead>
<tr>
<th>Table 2 - Treatment and prophylaxis of herpes infection in pregnant women</th>
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<tbody>
<tr>
<td>Antiviral</td>
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</table>
| First episode | Acyclovir 200 mg, 5 times a day  
  OR  
  Valacyclovir 500 mg every 12 hours (orally, for 10 days) |
| Recurrent episode | Acyclovir 200 mg, 5 times a day  
  OR  
  Valacyclovir 500 mg every 12 hours (orally, for 5 days) |
| Frequent recurrences | Acyclovir 400 mg every 8 hours |

...
Breastfeeding

The woman with herpetic lesions must follow standard precautions with hand hygiene and coverage of lesions during the breastfeeding period until they are in a phase of crust and breastfeeding is no longer counter-indicated. If the lesions are in the breast, the newborn should not be breastfed until the resolution of lesions, however, breastfeeding must be maintained in unaffected breasts.11

VARICELLA ZOSTER VIRUS (VZV) – HERPES-VIRUS 3

During pregnancy, the fetus can be infected with Varicella zoster virus (VZV) by transplacental transmission; however, the newborn can also be affected by contact with maternal vesicular lesions or respiratory secretions.17

Fetal infection generally occurs during the primary infection, i.e., chicken pox. Viremia in reactivation, such as zoster, is rare and related to patients with immunosuppression.17-19 Most infections show no manifestations; however, fetal infection can occur with zoster in the childhood.20

The first report of fetal lesions by varicella zoster occurred in 1947, called congenital varicella syndrome (CVS).21 Later, other publications revealed that the risk of fetal involvement is related to lower gestational age, occurring mainly at eight to 20 weeks of gestational age, however, there are rare studies that describe cases of up to 30 weeks.19,22-25 The prevalence of fetal disease is low, being less than 1% in the first two trimesters, when it is most frequent.20

Although fetal involvement is rare, the lesions are severe with reactivation that lead to retraction in affected dermatomes, locomotor system and central nervous system injuries, and high mortality.17,18 The low immune response may promote the dissemination and affected tissue lesions.20

There are reports on the use of prophylaxis with acyclovir after 36 weeks in pregnant women with recurrent manifestations. However, the effect of prophylaxis significantly reduces the recurrence of lesions and viral elimination although the effectiveness on reducing vertical transmission is not clarified yet.7,10,15 Cases of premature rupture of membranes and waiting conduct with the use of acyclovir have been described.5

Newborn

The treatment of the newborn should be performed with acyclovir and according to the form of clinical manifestation. In addition, patients with positive viral PCR research should also be treated because of the rapid disease progression and severity. The dose and time are set according to the infection clinical form and history of recurrences5,11-12; recommendations are presented in Table 3.

Some authors indicate the beginning of empirical treatment to newborn babies by vaginal birth to mothers with primoinfection, especially premature, and if there is a rupture of membranes over four to six hours regardless of symptoms. If the viral PCR research is negative, the medication can be suspended.11,12

White et al.14 reported the persistence of HSV positive PCR in liquor after 21 days of treatment and the need for continuity. Therefore, PCR repetition in the liquor is recommended in cases of central nervous system involvement after 21 days of treatment and acyclovir suspension only when negative.12

The literature records only a few cases in which there is a recurrence of lesions after discontinued treatment.9,10,16 Suppressive therapy with acyclovir (300 mg/m²/day at every 8 hours) can be used; it is recommended after the first episode of recurrence and should be maintained for periods of six months to a year because there is evidence of better neurological evolution.4

<table>
<thead>
<tr>
<th>Table 3 - Treatment of congenital infection by the herpes simplex virus</th>
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<tbody>
<tr>
<td><strong>Antiviral</strong></td>
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<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>- skin form</td>
</tr>
<tr>
<td>- disseminated form (without involvement of the central nervous system)</td>
</tr>
<tr>
<td><strong>Observation</strong> – new research for HSV DNA by PCR must be performed at 21 days in liquor and treatment should be suspended only when negative.</td>
</tr>
<tr>
<td>- encephalitis</td>
</tr>
<tr>
<td>- recurrence</td>
</tr>
</tbody>
</table>
In addition to intrauterine transmission, which can lead to CVS, transmission can occur during the peripartum period, called congenital or perinatal varicella. This occurs when the mother displays lesions five days before and two days after childbirth, and the newborn shows high risk of developing severe disease because there is no production and passage of antibodies to the fetus.19,20,26

**Diagnosis**

Chickenpox is a papulovesicular rash disease with typical evolution and allows clinical diagnosis. However, there may be a need for clarification by serology (IgM by ELISA or titration by FAMA). Research of virus by DNA PCR or monoclonal antibodies can be performed on lesion secretions and other materials.20,27

**Prophylaxis and treatment**

Prophylaxis with immune globulin11,17,20,28 after exposure or treatment if the expectant mother evolves with clinical manifestations16, 19, 26 is indicated because of the risk of serious illness and pneumonia caused by the virus, which increases 25 times and mortality reaches 20 to 45%. There is no evidence of benefits with regard to prevention of infection and/or fetal disease. In the case of newborns, prophylaxis is indicated if the mother presented the disease close to childbirth (five days before and two days after) with the goal of reducing risk of serious illness. In addition, premature infants younger than 28 weeks, regardless of maternal history, and older than 28 weeks, without a maternal history of prior varicella, should receive immune globulin if they are exposed.10,27,28

Acyclovir should be indicated for those newborns who despite the indication of immunoglobulin evolved with disease because there is a likelihood of serious neonatal disease.27 The conducts for the pregnant woman and newborn exposed to Varicella zoster, or have evolved with clinical disease, are presented in Table 4.

It is considered that the specific immunoglobulin is effective for newborns to mothers with disease manifested between five days before to 2 days after delivery, however, contact and respiratory precautions must be taken into account until the lesions are in the phase of crust, which occurs between five and seven days of disease evolution.20,27

If at the time of discharge, a brother or domiciliary contact is identified with the disease, the evolution to the crust phase in the lesions should be considered, however, the maternal history and use of prophylaxis must be evaluated. If the mother present previous history or positive serology, she can be discharged with her newborn. If the mother does not present previous history and has negative serology, immune globulin may be given to the mother and newborn before discharge.27

No conduct is defined for neonatal varicella acquired after birth, i.e. with postnatal exposure and disease manifested after the 10th day of life. In general, the evolution is more benign in these cases, especially if the mother has a previous history with the possibility of transfer of antibodies.27

**Table 4 - Conduct with pregnant women and newborns infected with Varicella zoster**

<table>
<thead>
<tr>
<th>Pregnant Prophylaxis</th>
<th>Specific immunoglobulin (VZIG ou VARIZIG).</th>
<th>Acyclovir orally for risk patients (smokers, pulmonary chronic disease, use of systemic corticoid or immune suppression due to basic disease).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Acyclovir</td>
<td>Orally – 80 mg/kg/day (maximum 3.200 mg/day) divided in 4 doses (maximum of 800 mg/dose every 6 hours) for 10 days. Intravenously – 10 mg/kg/dose every 8 hours (30 mg/kg/day) for 10 days (if severe disease or pulmonary form, must start from 1 to 6 days after beginning of lesions).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Newborn Prophylaxis</th>
<th>Immunoglobulin (VZIG or VARIZIG)</th>
<th>125 U/ 10 kg, intramuscular, maximum of 625 U, up to 96 hrs from contact. 800 mg, every 6 hours, orally, for 7 days, starting 7 days after exposure (secondary viremia).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Acyclovir</td>
<td>500 mg/m2/dose, EV, every 8 hours for 10 days.</td>
</tr>
</tbody>
</table>

Note 1 - Although there are no studies about the benefit from prophylaxis for pregnant women after 96 hours of exposure, the literature recommends specific immunoglobulin for immunocompromised children up to 10 days after contact with varicella.11

Note 2 - The vaccine may be used as prophylaxis of infection in women with no previous contact and at least one month before pregnancy.
Breastfeeding

Breastfeeding should not be permitted for women with active lesions to avoid contact and transmission of VZV to her newborn. However, breast milk must be milked and offered to the child. In addition, the mother with indication should receive specific immunoglobulin. Recent mothers’ vaccination as prophylaxis after contact can also be considered.11,27

Cytomegalovirus (CMV) – Herpes-Virus 4

Cytomegalovirus (CMV) is the most frequent agent of congenital infection in humans, occurring in 0.2-2.2% of all live births.29 Its prevalence in the general population increases with age and is influenced by geographical location and cultural and socioeconomic factors. In developing countries, 80% of the population acquires the disease until the three years of life and virtually all have been infected by adulthood while in developed countries this rate is 40-60%.30

CMV is a DNA virus in the Herpesviridae family characterized by the ability to sustain replication for long periods or remain in latency. It is excreted in various sites (blood, urine, milk, saliva, semen, uterine cervix secretions, and others), allowing various forms of transmission. Contaminated food can also have a role in the transmission because it has been demonstrated that CMV maintains infectivity for hours on plastic surfaces. Vertical transmission occurs via transplacental (congenital infection), birth canal, or through breast milk (perinatal infection). Horizontal transmission is the result of contact with secretions containing the virus, usually saliva or urine; however, sexual transmission is also possible between young and sexually active adults. The infection can also be transmitted iatrogenically by blood transfusion or organ transplant. The viral shedding is prolonged; approximately half of those infected by congenital transmission presents viruria for six years.29

Unlike rubella and toxoplasmosis, congenital cytomegalovirus can occur both after maternal primary infection and after recurrence of infection (reactivation or re-infection). There is a significant number of CMV strains, similar to each other, so that the primary infection can provide partial immunity against other strains providing less intrauterine transmission and low risk of severe fetal infection in case of reinfection.31 The majority of children affected is asymptomatic, and 10 to 15% have long-term sequelae.32 The flowchart in Figure 2, adapted from Raynor33, outlines the possible clinical evolution of the disease.

Clinical manifestations

Clinical manifestations can be acute (symptomatic form) or late (sequelae). Half of symptomatic newborns presents the most severe forms, known as “cytomegalic inclusion disease” (Figure 3A) characterized by jaundice, hepatosplenomegaly, petechiae, microcephaly, microcephaly, chorioretinitis, and cerebral calcifications (Figures 3B and 3C). Other findings include prematurity, restricted intrauterine growth, increased transaminases, thrombocytopenia, hiperproteinorraquia, and evidence of hemolysis. The other newborns have these symptoms alone or in various combinations. The main sequelae found are neurological and auditive occurring even in asymptomatic children at birth.30-32

CMV is the most common cause of non-hereditary sensorineural hearing loss in children.33-36 A study with 190 symptomatic children showed that petechiae and restricted intrauterine growth are independent risk factors for hearing loss and that the involvement of the central nervous system at birth does not predict hearing loss.34

Noyola et al.35 concluded in a study with 41 symptomatic children that microcephaly at birth is the most specific predictor of cognitive deficit in symptomatic children and the combination of cranial computed tomography (CT) and normal cephalic perimeter implies in good cognitive prognosis.

Diagnosis

Prenatal

The CMV research is not part of the serological screening performed in prenatal care in many countries including Brazil. The virus is widely distributed in the environment and most primoinfections occur even during childhood, with low morbidity and absence of fetal therapy effective for pregnant women. Although not recommended in public health actions, the CMV screening during pregnancy has been suggested by some authors37-38 as presented in Table 5.
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Post-natal

The newborn diagnosis should be performed as early as possible, preferably before two to four weeks of life. It is difficult to differentiate intrauterine and perinatal infection after three weeks of life unless demonstrations such as chorioretinitis and ventriculitis are present. The tests proposed for etiological definition of infection are presented in Table 6.

In addition to the propedeutics for confirmatory diagnosis, the investigation of involvement of target organs should be performed, including CBC, liver function tests, ultrasound transfontanelar ultrasound (if necessary, CT scan of the skull), ophthalmoscopy, and audiometry. RNs with confirmatory diagnosis and evidence of involvement of these organs shall be subjected to examination of liquor (with routine and PCR...
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research for CMV in liquor to evaluate central nervous system involvement). The therapeutic decision should consider the involvement of these organs.11,32-34

**Table 6** - Propedeutics indicated for the diagnosis of congenital cytomegalovirus infection

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Description</th>
<th>Sensitivity/Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral culture</td>
<td>Gold standard for CMV diagnosis</td>
<td>100%</td>
</tr>
<tr>
<td>PCR-DNA</td>
<td>Extremely sensitive, detecting minimal quantities of viral DNA in various clinical specimens</td>
<td>70-100%</td>
</tr>
<tr>
<td>Serology</td>
<td>Sensitivity varies with the method used and the time of collection. Should be performed in the first days of life, paired with maternal serology and subsequently serially. Various methods can be used: complement fixation and indirect hemagglutination detect predominantly IgG antibodies. The immunofluorescence (IFI) has the advantage of detecting IgM (45% sensitivity). ELISA, in addition to more sensitivity (75%) and availability of commercial reagents. To diagnosis of the congenital form, serology should be done in the first three weeks of life, paired with maternal serology.</td>
<td></td>
</tr>
<tr>
<td>Antigenemia pp65</td>
<td>CMV antigen detection by monoclonal antibody (IFI)</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Treatment**

Currently, the treatment of CMV congenital infection has been indicated for symptomatic children identified in the first month of life. The antiviral used is ganciclovir, a guanosine analog with structure similar to acyclovir but with 30 times wider action against CMV. Several studies have been conducted, however, doses and treatment time are still under investigation.11 Some studies showed treatment benefit due to the stopped progression of hearing loss.30-41 It is known that ganciclovir decreases or prevents viral multiplication and inhibits spread, however, viral replication restart after discontinuation of therapy, therefore, the maintenance treatment with valganciclovir has been questioned.30

In general, ganciclovir is well tolerated, eventually causing nausea, vomiting, and headache with its administration. The main adverse effect is myelotoxicity requiring monitoring with CBC, ions, and kidney and liver function on alternate days during induction, and weekly during maintenance.41 Table 7 presents the inclusion and exclusion criteria for treatment in addition to recommendation guidelines for drug administration and laboratory control of treatment.11,32,36,40-42

It should be noted that studies have been conducted with the use of specific hiperimmune immunoglobulin in infected pregnant women and assessment of involvement and symptomatology of the fetus and newborn.44-46

**Table 7** - Inclusion and exclusion criteria for the treatment of congenital cytomegalovirus infection and guidelines for the administration and monitoring acyclovir

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Inclusion criteria for treatment</td>
<td>Symptomatic NB with evidence of CNS involvement, including intracranial calcifications, microcephaly, cortical atrophy, altered cerebrospinal fluid, chorioretinitis, and deafness. NB with interstitial pneumonitis by CMV. Age &lt;1 month at the time of diagnosis. Weight &lt; 1,000 grams.</td>
</tr>
<tr>
<td>2- Exclusion criteria for treatment</td>
<td>Asymptomatic NB. Symptomatic RNs without CNS involvement except interstitial pneumonitis or severe/widespread forms (pulmonary, gastrointestinal/liver, and bone marrow involvement).</td>
</tr>
<tr>
<td>3- Drug administration</td>
<td>Ganciclovir, dose of 8 to 12 mg/kg/day, every 12 hours, diluted in 9% NaCl or 5% SGI, dilution of 10 mg/mL, slow infusion in one hour, presentation in ampule 500 mg/10 mL.</td>
</tr>
<tr>
<td>4- Dose modification</td>
<td>Neutropenia (&lt;500 cells/mm³) e thrombocytopenia (&lt;50,000 cells/mm³): dose reduction to 4 a 6 mg/kg/day.</td>
</tr>
<tr>
<td>5- Laboratory control during treatment</td>
<td>Complete blood count with platelet count, urea and creatinine, aminotransferases and serial bilirubin at least weekly.</td>
</tr>
</tbody>
</table>

Breastfeeding

Breastfeeding is allowed although there is concern in CMV transmission through breast milk to premature infants less than 32 weeks or less than 1,500 g; there are few reported cases of newborns with perinatal acquisition of viruses who have evolved with acute symptomatic disease (with demonstrations of dissemination particularly thrombocytopenia, neutropenia, and hepatic and pulmonary involvement), appar-
ently without sequelae. Accordingly, the suspension of breast milk should not be a routine due to the benefits of breast-feeding, however, it is a practice to be considered in cases of confirmed acute maternal disease and if the newborn present a high risk for the disease. Pasteurized breast milk can be used in these cases.11,17

CONCLUSION

The importance of prevention and early diagnosis of herpes-virus infections are emphasized during pregnancy and in newborns to allow investigation of affected target organs and specific treatments when indicated. The use of polymerase chain reaction for these viruses has been widely adopted in various clinical specimens, with high sensitivity and specificity, and should be included in the diagnostic investigation.

REFERENCES


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