European Journal of Obstetrics & Gynecology and Reproductive Biology 224 (2018) 93–101

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review article

Prevention and management of genital herpes simplex infection during pregnancy and delivery: Guidelines from the French College of Gynaecologists and Obstetricians (CNGOF)

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ARTICLE INFO

Article history:
Received 19 February 2018
Received in revised form 6 March 2018
Accepted 8 March 2018

Keywords:
First episode of genital herpes
Recurrence
Prophylactic treatment
Mode of delivery

ABSTRACT

Objective: Identify measures to diagnose, prevent, and treat genital herpes infection during pregnancy and childbirth as well as neonatal herpes infection.
Materials and methods: Bibliographic search from the Medline and Cochrane Library databases and review of international clinical practice guidelines.
Results: Genital herpes lesions are most often due to HSV-2 (LE2). The risk of HSV seroconversion during pregnancy is 1–5% (LE2). Genital herpes lesions during pregnancy in a woman with a history of genital herpes is a recurrence. In this situation, there is no need for virologic confirmation (Grade B). In pregnant women with genital lesions who report they have not previously had genital herpes, virological confirmation by PCR and identifying the specific IgG type is necessary (professional consensus). A first episode of genital herpes during pregnancy should be treated with aciclovir (200 mg 5 times daily) or valaciclovir (1000 mg twice daily) for 5–10 days (Grade C), and recurrent herpes during pregnancy with aciclovir (200 mg 5 times daily) or valaciclovir (500 mg twice daily) (Grade C). The risk of neonatal herpes is estimated at between 25% and 44% if a non primary and primary first genital herpes episode is ongoing at delivery (LE2) and 1% for a recurrence (LE3). Antiviral prophylaxis should be offered to women with either a first or recurrent episode of genital herpes during pregnancy from 36 weeks of gestation until delivery (Grade B). Routine prophylaxis is not recommended for women with a history of genital herpes but no recurrence during pregnancy (professional consensus). A cesarean delivery is recommended if a first episode of genital herpes is suspected (or confirmed) at the onset of labor (Grade B) or if it occured less than 6 weeks before delivery (professional consensus) or in the event of premature rupture of the membranes at term. When a recurrence of genital herpes is underway at the onset of labor, cesarean delivery is most likely to be considered when the membranes are intact and vaginal delivery in cases of prolonged rupture of membranes (professional consensus). Neonatal herpes is rare and mainly due to HSV-1 (LE3). In most cases of neonatal herpes, mothers have no history of genital herpes (LE3). When neonatal herpes is suspected, various samples (blood and cerebrospinal fluid) for HSV PCR must be taken to confirm the diagnosis (professional consensus). Any newborn with suspected neonatal herpes should be treated with intravenous acyclovir (20 mg/kg 3 times daily) (grade A) before the PCR results are available (professional consensus). The duration of the treatment depends on the clinical form (professional consensus)

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https://doi.org/10.1016/j.ejogrb.2018.03.011
0301-2115/

Conclusion: There is no formal evidence that it is possible to reduce the risk of neonatal herpes in genital herpes during pregnancy. However, appropriate care can reduce the symptoms associated with herpes and the risk of recurrence at term, as well as cesarean rate because of herpes lesions.

Contents

Introduction and methods [1–3]

The sponsor (the French College of Gynecologists and Obstetricians (CNGOF)) appointed a steering committee (Appendix A) to define the exact questions to be put to the experts, to choose them, follow their work and draft the synthesis of recommendations resulting from this work [1]. The experts analyzed the scientific literature on the subject to answer the questions raised. A literature review identified the relevant articles through mid-2017 by a search of the MEDLINE database and the Cochrane Library. The search was restricted to articles published in English and French [2,3]. Priority was given to articles reporting results of original research, although review articles and commentaries were also consulted. Guidelines published by organizations or institutions such as the American College of Obstetricians and Gynecologists (ACOG) [4], the Royal College of Obstetricians and Gynaecologists (RCOG) [5], the Canadian Society of Gynaecology and Obstetric (SOGC) [6], the Australasian Society for Infectious Diseases (ASID) [7], the Canadian Paediatric Society (CPS), the US Centers for Disease Control and Prevention (CDC) [8], the government of South Australia Maternal, Obstetrics and Gynaecology Community of Practice (South Australia) [9], the European region of the International Union Against Sexually Transmitted Infections (IUSTI) [10], and the Canadian Paediatric Society [11]. Additional studies were located by reviewing bibliographies of identified articles. For each question, each overview of validated scientific data was assigned a level of evidence based on the quality of its data, in accordance with the framework defined by the HAS (French Health Authority) [3], summarized below.

Quality of evidence assessment

LE1: very powerful randomized comparative trials, meta-analyses of randomized comparative trials;

LE2: not very powerful randomized trials, well-run non-randomized comparative studies, cohort studies;

LE3: case-control studies;

LE4: non-randomized comparative studies with notable biases, retrospective studies, cross-sectional studies, and case series.

A synthesis of recommendations was drafted by the organizing committee based on the replies given by the expert authors. Each recommendation for practice was allocated a grade, defined by the HAS as follows:

Classification of recommendations

Grade A: Recommendations are based on good and consistent scientific evidence

Grade B: Recommendations are based on limited or inconsistent scientific evidence

Grade C: Recommendations are based primarily on consensus and expert opinion

Professional consensus: In the absence of any conclusive scientific evidence, some practices have nevertheless been recommended on the basis of agreement between the members of the working group (professional consensus).

All texts were reviewed by persons not involved in the work, i.e., practitioners in the various specialties (Appendix A) concerned and working in different situations (public, private, university, or non-university establishments). Once the review was completed, changes were made, if appropriate, considering the assessment of the quality of the evidence.

The original long texts in French are cited [12–16], but their individual references are not included here in view of the enormous space they would occupy in this article intended to summarize the guidelines.

Definitions [12]

The different stages of the history of a herpes infection are defined virologically and clinically.

Virologically, seroconversion corresponds to the presence of G immunoglobulins (IgG) in a patient who previously had none.

Primary and non-primary infections are defined as follows:

Primary infection:

The first episode of a genital herpes (Herpes Simplex Virus 1 (HSV-1) or Herpes Simplex Virus 2 (HSV-2)) in a patient who has never previously had herpes, regardless of the site.

Non-primary infection:

The first episode of HSV-1 genital herpes in a patient who has already had an HSV-2 infection or

The first episode of HSV-2 genital herpes in a patient who has already had an HSV-1 infection.

These stages differ in terms of viral shedding and recurrence.

Asymptomatic viral shedding: the detection of HSV-1 or HSV-2 in the absence of functional signs or lesions visible to either the patient or the doctor.

Recurrence: period of clinical viral replication in a woman who has already had at least one previous episode.

Clinical definitions

Doctors confront two different situations in clinical practice, which will be developed in these Clinical Practice Guidelines (Fig. 1):

1- A genital lesion apparently herpes, in a patient with no past history of genital herpes; it can correspond to a first episode primary herpes, or to an non-primary first episode or even to a recurrence when a primary infection and even past recurrences were not noticed. The newborn is at greatest risk from an initial primary infection.

2- The demonstration of clinical genital lesions in a woman who already has a history of herpes infection at that site is a recurrence. Genital coinfections of HSV-1 and HSV-2 (as non-primary infections) are rare and will be considered to be recurrences.

Epidemiology, disease manifestations, prevention, and screening [12]

Symptoms can be atypical (LE2). No studies have compared clinical symptoms during and outside of pregnancy. Indirect comparisons do not appear to show that the clinical expression of genital herpes during pregnancy differs in any particular respect from those outside pregnancy (professional consensus). Genital infection is most often due to HSV-2, but the prevalence of HSV-1 infection has been rising in recent years (LE2). Around 70–80% of pregnant women have a history of HSV infection, although its location (genital or labial) and clinical history vary; in most cases, it is type 1 (LE2). In woman with recurrent genital herpes during pregnancy, the prevalence of clinical lesions at delivery in the absence of treatment is on the order of 14.3% compared with 36% for initial infections, again without specification of the viral type (LE4). The prevalence of lesions during delivery in the absence of recurrence during pregnancy is not known. In women seropositive for either viral type, asymptomatic herpes shedding detected by polymerase chain reaction (PCR) is on the order of 4–10% (LE3). HSV-2 is more prevalent than HSV-1 (LE2). This shedding rises in women who are HIV+ (on the order of 20–30%) (LE2). The risk of HSV seroconversion during pregnancy is on the order of 1–5% (LE2), but can reach 20% in serodiscordant couples (LE2). The principal risk factor for HSV contamination during pregnancy is the existence of another sexually transmitted infection (STI) (LE2), the recency of the relationship (LE2), and the partner's history of herpes (LE2). Taking a history is not always sufficient to learn about previous herpes infections in either the patient or her partner (LE2). In the absence of a lesion, the clinical examination has a strong negative predictive value (LE2). In the case of an initial lesion the positive predictive value of clinical examination is fairly high, but PCR confirmation is required in view of the importance of the specific type in determining the most appropriate management (Grade B).

Fig. 1. Different Situations in clinical practice.

Herpes hepatitis is rare and can be serious (LE4). It must be considered in all cases of unexplained hepatic cytolysis during pregnancy (professional consensus). In any clinical situation suggesting febrile encephalitis, herpes encephalitis must be considered (grade C), and an antiviral treatment begun as early as possible (professional consensus). No association has been established between herpes infection and miscarriages (LE3), but untreated herpes infection does appear to be associated with preterm delivery (LE3). This association may disappear for treated infections (LE3). Fetal herpes disorders are rare and may be due to either primary or non-primary infections, to HSV-1 or -2, and be accompanied or not by maternal symptoms (LE4).

No evidence exists to justify the recommendation of any specific procedures for antenatal fetal diagnosis in cases of maternal herpes infection during pregnancy (professional consensus). Condom use reduces the risk of initial infection in non-pregnant women (LE3). In the case of serodiscordant couples (F−, M+), condom use can be recommended during the third trimester in the absence of a clinical lesion (Grade C). When a lesion is present, sexual relations, including orogenital, should be avoided, especially close to term (professional consensus). No usable vaccine is currently available (professional consensus). The cost of HSV serology of both parents would be high, and neonatal herpes cases are very rare in France. Moreover, the father would need to be present, to answer questions on this delicate topic accurately, and the results would have to be available promptly. To be effective, this screening would also have to be exhaustive, which appears impossible. No clinical study seems to have assessed serologic screening strategies. For all these reasons, there is not sufficient evidence to justify a routine screening policy during pregnancy (professional consensus).

Tools for virologic diagnosis [13]

PCR is recommended over culture and antigen detection to enable direct virus detection (professional consensus). Nonetheless, PCR is not currently included in the official French classification of laboratory procedures (NABM) and is therefore not reimbursed by the national health insurance fund (NHIF). Prescribers should inform themselves of the technique used by laboratories to ensure the appropriateness of their sampling method and the conditions of transport (professional consensus). Reciprocally, and at the latest, when PCR is included in the NABM, laboratories should implement the techniques having the best sensitivity and specificity values and best adapted to the organization of care, in particular for time until result availability (professional consensus).

HSV serology must search for type-specific IgG (grade B). In the absence of a lesion, this will enable determination of the woman's immune status (grade B). For women with a lesion, serological testing must be ordered only in clinical situations of a herpes episode occurring in a woman with no history of genital herpes, to differentiate a primary first episode of genital herpes from either an non-primary first episode of genital herpes, or a potential recurrence (professional consensus). IgM research has no utility in the diagnosis of maternal genital herpes or neonatal herpes (Grade C). When herpes lesions appear during pregnancy in a woman reporting no history of herpes, a primary first episode or a non-primary first episode must be distinguished from a recurrence of an first episode that was unnoticed. This distinction must be based on direct detection of the lesion (by PCR or, if unavailable, by culture) and type-specific serology (only in IgG) (Grade C). In women with a past history of genital herpes and without a lesion or prodromal signs, regardless of term of the pregnancy, of any antiviral prophylaxis administered (or not) and of the interval between the last recurrence and delivery, there is no reason to recommend either serologic testing or genital sampling to look for asymptomatic viral shedding (professional consensus). Similarly, sampling for virologic confirmation of herpes is not recommended for pregnant women with a past history of genital herpes and a standard clinical presentation, including at the onset of labor or in cases of rupture of the membranes (professional consensus). On the other hand, sampling for virologic confirmation is recommended for women with a past history of genital herpes who have an atypical lesion or an unusual clinical presentation during pregnancy, (professional consensus). Finally, at the onset of labor or in cases of rupture of the membranes, prodromal signs, an atypical lesion, or an unusual clinical presentation, sampling for virologic confirmation can be performed when a rapid result is possible and might modify obstetric management (professional consensus) (Fig. 2).

The virologic diagnosis of neonatal herpes must be based on direct detection of the virus by PCR as soon as neonatal herpes is suspected (symptomatic newborn), preferably before the start of antiviral treatment but without delaying it, or after 24 h of life if the newborn is at (major or minor) risk of neonatal herpes but asymptomatic (professional consensus). The samples must at a minimum include a peripheral blood sample, together with cerebrospinal fluid (CSF) and other peripheral samples (or potential lesions) in newborns with a major risk of neonatal herpes (maternal primary first episode or non-primary first episode), newborns with suspected neonatal herpes (symptomatic newborn), or PCR that is HSV+ for the first samples (professional consensus). If the PCR is negative but neonatal herpes is strongly suspected, these samples must be repeated and include multiple sites (professional consensus).

Suspected genital herpes lesion in a pregnant patient without a past history of genital herpes [14]

In case of suspected genital herpes lesion in a pregnant patient without a past history of genital herpes, direct detection of the lesion (by PCR or, if unavailable, by culture) and type-specific serology virologic diagnosis are recommended in order to confirm that it's a first episode of genital herpes (Grade C).

No study has reported the effectiveness of antiviral treatment on local symptoms in first episode of genital herpes in pregnant women. Among men and nonpregnant women, antiviral treatment by aciclovir 200-mg tablets, taken orally 5 times daily for 5–10 days, depending on clinical status, may reduce the duration of symptoms and lesions in a first episode of genital herpes, especially a primary herpes infection (LE3). Valaciclovir 500 mg provides an apparently similar effectiveness with only 2 tablets daily (LE3). There is no evidence to support intravenous (IV) rather than oral administration of aciclovir in uncomplicated genital herpes (expert opinion). Topical antiviral treatments are less effective than systemic pathway treatments (LE3).

For disseminated herpes, intravenous administration of antiviral treatment is recommended as early as possible, together with a multidisciplinary management by gynecologist-obstetricians and infectious disease specialists (professional consensus). The current data about the potential fetal and neonatal side effects of antiviral treatment by aciclovir or valaciclovir during pregnancy are reassuring (LE2).

Initiation of antiviral treatment is recommended for a first episode of genital herpes during pregnancy (Grade C). There are more data about the safety of aciclovir, but valaciclovir can also be prescribed because of the simplicity of its use (professional consensus). Treatment is oral aciclovir, with a 200-mg tablet five times daily, or valaciclovir, with two 500-mg tablets twice a day, both for 5–10 days depending on clinical state (Grade C).

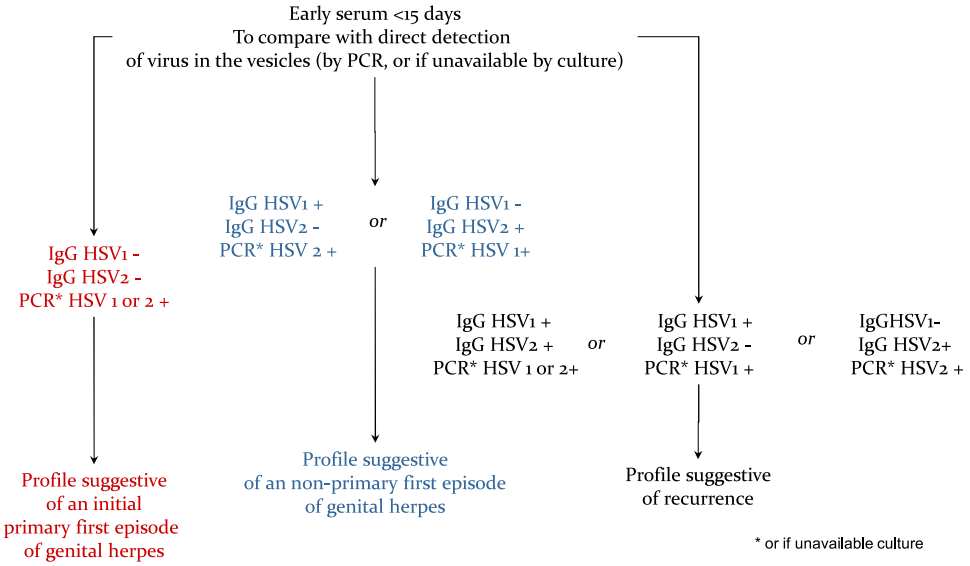

Fig. 2. Interpretation of virological tests after clinical signs of genital HSV.

In a suspected first episode of genital herpes, antiviral treatment can begin without awaiting laboratory test results, depending on clinical status and expected time to results (professional consensus). Herpes is an STI, and the principal risk factor of an initial herpes infection during pregnancy is the existence of another STI (LE2). Genital herpes may increase the risk of HIV transmission to both the partner and the newborn (LE4). Condom use reduces the risk of STI transmission, especially of herpes (LE2). In initial episodes of genital herpes during pregnancy, an HIV serology test is recommended (Grade B) as well as screening for other STIs, based on context (professional consensus). Women should be advised to abstain from sexual relations in the presence of ulcerations or symptoms suggestive of genital herpes, to avoid transmitting herpes to their partner (professional consensus).

Among women with a first episode of genital herpes during pregnancy, prophylactic treatment has shown no benefits in reducing the risk of neonatal herpes, but antiviral prophylaxis is nonetheless recommended at 36 weeks of gestation until delivery, to reduce the risk of cesarean because of herpes lesions (Grade B). Treatment may begin at 32 weeks' gestation for twin pregnancies, because of their high risk of preterm delivery (professional consensus). Similarly, antiviral treatment can be started early in some situations at high risk of preterm delivery (professional consensus). This treatment uses oral aciclovir (two 200-mg tablets three times a day) or valaciclovir (a 500-mg tablet, twice a day) (Fig. 3).

The risk of neonatal herpes is higher when the first episode of genital herpes occurs near delivery, because of the risk of viral shedding and the absence of maternal seroconversion, which is protective for the newborn (LE2). It can reach 44% in primary infections and 25% in non-primary first episodes (LE2). The time necessary for seroconversion after a first episode of genital herpes varies but is most often less than 6 weeks (LE3). When lesions or signs suggestive of a first episode of genital herpes (or a confirmed first episode) are present at labor, cesarean delivery is recommended because it probably reduces the risk of neonatal herpes (Grade C). Similarly, a cesarean delivery is recommended when delivery takes place less than 6 weeks after a first episode of genital herpes (professional consensus). Vaginal delivery is possible when a first episode of genital herpes during pregnancy is treated appropriately with prophylactic antiviral treatment and with no lesions or suggestive signs at labor. It is even possible when the initial episode occurred during the third trimester, as long as the delivery takes place at least 6 weeks afterwards (professional consensus). Cesarean delivery is recommended when lesions or symptoms suggestive of an initial episode of genital herpes (or a confirmed initial episode) are present and rupture of the membranes occurs after 37 weeks of gestation. If possible, it should take place in the 4 h after rupture (professional consensus), because this might reduce the risk of neonatal herpes (expert opinion). Despite the absence of data in the literature assessing the interest of a cesarean delivery in this situation (LE4), a cesarean delivery rather than a vaginal delivery is recommended (professional consensus) in cases of prolonged rupture of the membranes at term and even during labor, because a first episode of genital herpes at delivery is the situation at highest risk of neonatal herpes (LE2). In case of premature rupture of the membranes and first episode of genital herpes, multidisciplinary management is required and must consider principally the issue of gestational age (professional consensus). The earlier the gestational age at membrane rupture, the more likely that expectant management with antiviral treatment will be preferred (professional consensus). If the delivery takes place more than 6 weeks after the infectious episode, vaginal delivery is possible in cases of premature rupture of the membranes, in the absence of lesions or suggestive signs during labor (professional consensus). Should a maternal herpes lesion be discovered after delivery, assessment of the risk of transmission to the newborn will enable the pediatrician to adapt neonatal management appropriately (professional consensus). Antiviral treatment of the mother can be administered according to the standard procedures (Grade C).

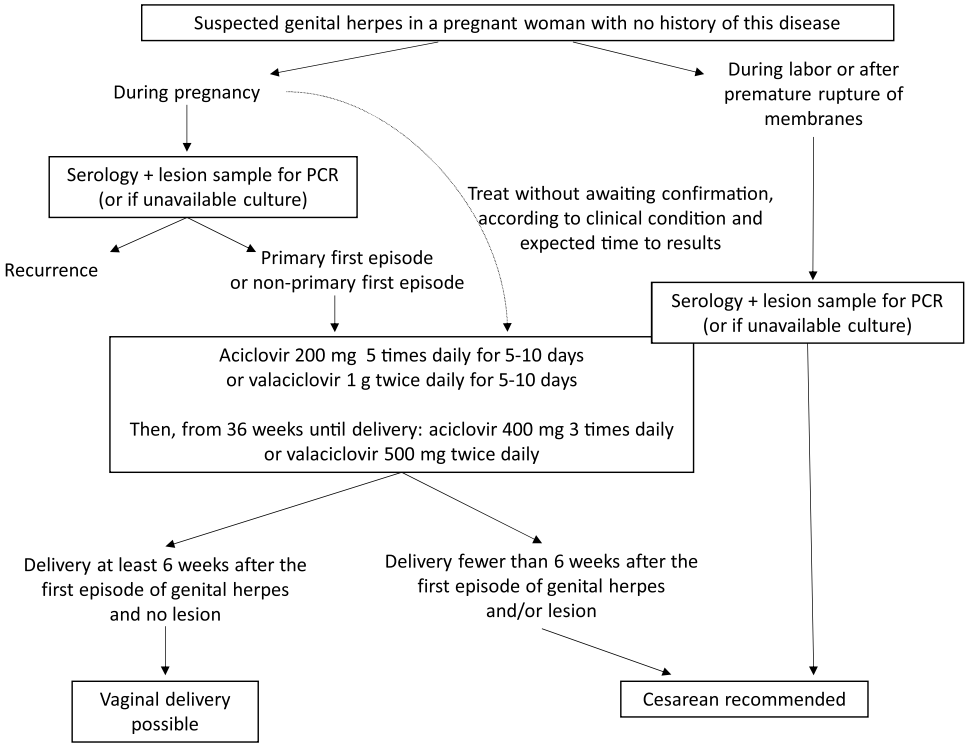

Fig. 3. Algorithm for the management of woman without a past history of genital herpes.

Suspected herpes lesion in a pregnant women with a past history of genital herpes [15]

If a pregnant woman with a past history of genital herpes has a typical lesion and usual clinical presentation, sampling (swabbing) it to confirm it is a herpes lesion is not recommended (professional consensus). If the lesion is atypical, however, virologic confirmation is recommended by swabbing the lesion to verify the presence of the virus by PCR or culture (professional consensus). The probability that a herpes lesion is associated with an non-primary first episode of genital herpes is very low in a woman with known history of genital herpes. A sample is therefore unnecessary to consider the lesion a recurrence (Grade C).

No study has reported the effectiveness of antiviral treatment of local symptoms in the recurrence of genital herpes in pregnant women. Antiviral treatment with aciclovir (200 mg 5 times daily) or valaciclovir (500 mg twice daily) can be proposed to reduce the duration and intensity of symptoms during the prodrome or recurrence of genital herpes in the 24 h after the beginning of the eruption in a pregnant woman disabled by these symptoms (Grade C). Nonetheless the treatment's benefit is modest; it reduces the duration of viral shedding and the duration of symptoms by 1–2 days (LE3).

The treatment is either oral aciclovir, a 200-mg capsule 5 times a day for 5 days, or one 500-mg capsule of valaciclovir twice a day for 5 days (Grade C). Although no benefit has been shown for prophylactic treatment to reduce the risk of neonatal herpes, it is nonetheless recommended that women with at least one recurrence during pregnancy begin antiviral prophylaxis at 36 weeks of gestation until delivery, to reduce the risk of cesarean delivery because of herpes lesions (Grade B). The antiviral agents recommended are aciclovir at a dosage of 400 mg orally 3 times a day or 500 mg of valaciclovir twice a day until delivery. In situations at risk of preterm birth (threatened preterm delivery, multiple pregnancy), prophylaxis can begin earlier (professional consensus). The benefit of prophylactic treatment has not been demonstrated for women with a history of genital herpes whose last recurrence preceded the pregnancy. Antiviral prophylaxis is therefore not recommended for women who have not had a recurrence during pregnancy, but it should be considered if recurrences were frequent and recent before the pregnancy (professional consensus). The risk of neonatal herpes in the case of recurrence at delivery is estimated at approximately 1% (LE3). It is not recommended to take a sample of a lesion to verify that it is HSV from women with a known history of genital herpes and a typical lesion at the onset of labor or with ruptured membranes (professional consensus). If the lesion is atypical or prodromal signs are present at the onset of labor or after rupture of the membranes, virologic confirmation can be sought by swabbing the lesion to test for the virus by PCR, but only if the result can be provided on an emergency basis and when the result might modify the obstetric management (professional consensus). The risk of neonatal herpes from asymptomatic viral shedding in a woman with a history of genital herpes is low (LE3), and the literature contains no data enabling us to assess the relevance of an emergency PCR for asymptomatic women. PCR testing is therefore not recommended at the onset of labor or after premature rupture of the membranes in the absence of either a lesion or prodromal signs in a woman with a history of herpes recurrence, regardless of whether or not she received antiviral prophylaxis and of the interval between the last recurrence and delivery (professional consensus).

Similarly the literature does not justify the recommendation of one type of delivery over another in cases of prodromal signs or of a clinical genital herpes lesion in women with a past history of herpes at the onset of labor (professional consensus). A cesarean delivery will be considered especially when the membranes are intact or delivery is preterm or the mother is HIV+ (professional consensus). Inversely, vaginal delivery is especially likely after either prolonged rupture of the membranes or 37 weeks of gestation, and for mothers not HIV+ (professional consensus). For woman with a past history of genital herpes, but no lesion or prodromal signs, there is no contraindication to fetal scalp sampling or electrode use, to operative vaginal delivery, or to artificial rupture of the membranes. Labor is managed as usual (professional consensus). Data about vaginal delivery in women with a herpes recurrence during labor are inadequate to determine whether fetal scalp pH testing or electrode use or an operative vaginal delivery increases the risk of neonatal herpes, or whether antiviral treatment is effective in reducing the risk of neonatal herpes (expert opinion). Nonetheless, if vaginal delivery is otherwise considered appropriate, extrapolation of data for primary first episode justifies a recommendation against fetal scalp testing or electrode use and to limiting amniotomy to validated indications. There is however no contraindication to operative vaginal delivery (professional consensus). If herpes recurs at perianal, buttock, or thigh sites, meticulous examination of the birth canal is recommended to detect any genital herpes lesion (professional consensus). In the absence of a concomitant genital lesion, the risk of genital viral shedding is low. Taking samples to test for HSV is therefore not recommended (professional consensus). Only obstetric considerations should govern the determination of the management of delivery (professional consensus). In recurrent herpes in a woman with a premature rupture of the membranes before 37 weeks, the risks associated with preterm delivery and with neonatal herpes must be weighed. The data from the literature are insufficient for a determination of the gestational age at which induction of labor should be recommended over expectant management (professional consensus). In view of the effectiveness of antiviral treatment in reducing viral shedding, treatment with aciclovir or valaciclovir is recommended (professional consensus). Data are insufficient to justify any different management than that usually applied in cases of premature rupture of the membranes before 37 weeks (professional consensus) (Fig. 4).

Epidemiology, clinical manifestations, and management of neonatal herpes [16]

Neonatal herpes is rare (incidence: 3/100,000 births) (LE3); the most recent studies show a predominance of the HSV-1 serotype (LE3). The principal risk factors for mother-child transmission are maternal primary first episode of genital herpes and the HSV-1 serotype (LE3). The effect of antenatal prophylaxis by aciclovir or valaciclovir on the risk of mother-child transmission is unknown. Mortality is high for neonatal herpes and varies with its clinical form (mortality with treatment: mucocutaneous form 0%, affecting the central nervous system (CNS) 6%, disseminated 31%) (LE3). Early administration of intravenous high-dose aciclovir (60 mg/kg/d) reduces mortality if the CNS is affected (LE3).

Morbidity is principally neurological (cognitive delay or impairment, blindness, epilepsy, or neuromotor effects) (LE3) and depends on the clinical form (LE3). Data about the risk of recurrence in childhood are sparse, especially since the development of suppressive treatment by oral aciclovir (expert opinion). Most cases of neonatal herpes are not associated with a maternal history of genital herpes (LE3). Fever and typical vesicular lesions can be absent at admission and even during the course of the disease (LE3).

The diagnosis must be considered for neonates with any atypical clinical situation (respiratory, neurological or unexplained bleeding) or antibiotic-resistant sepsis (Grade C). All in all, from the

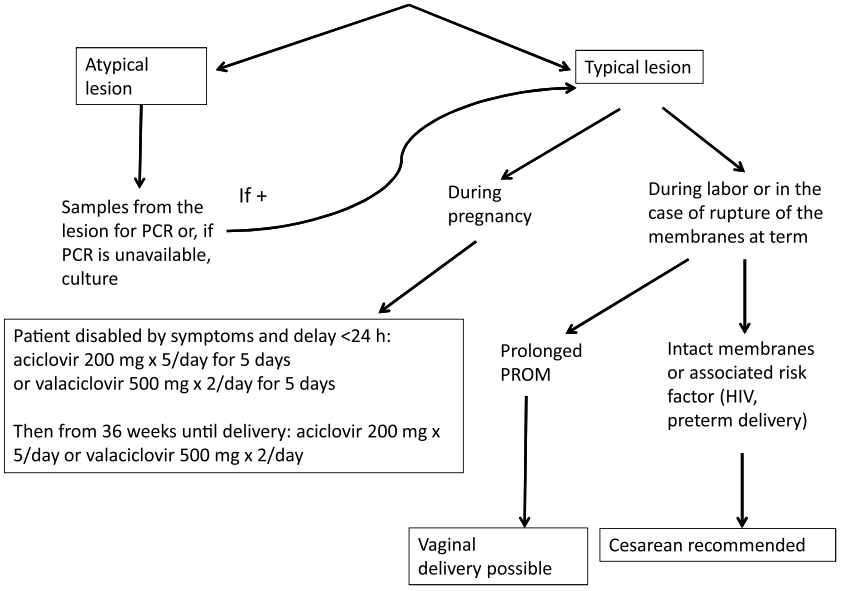

Fig. 4. Algorithm for the management of woman with genital recurrent herpes during pregnancy.

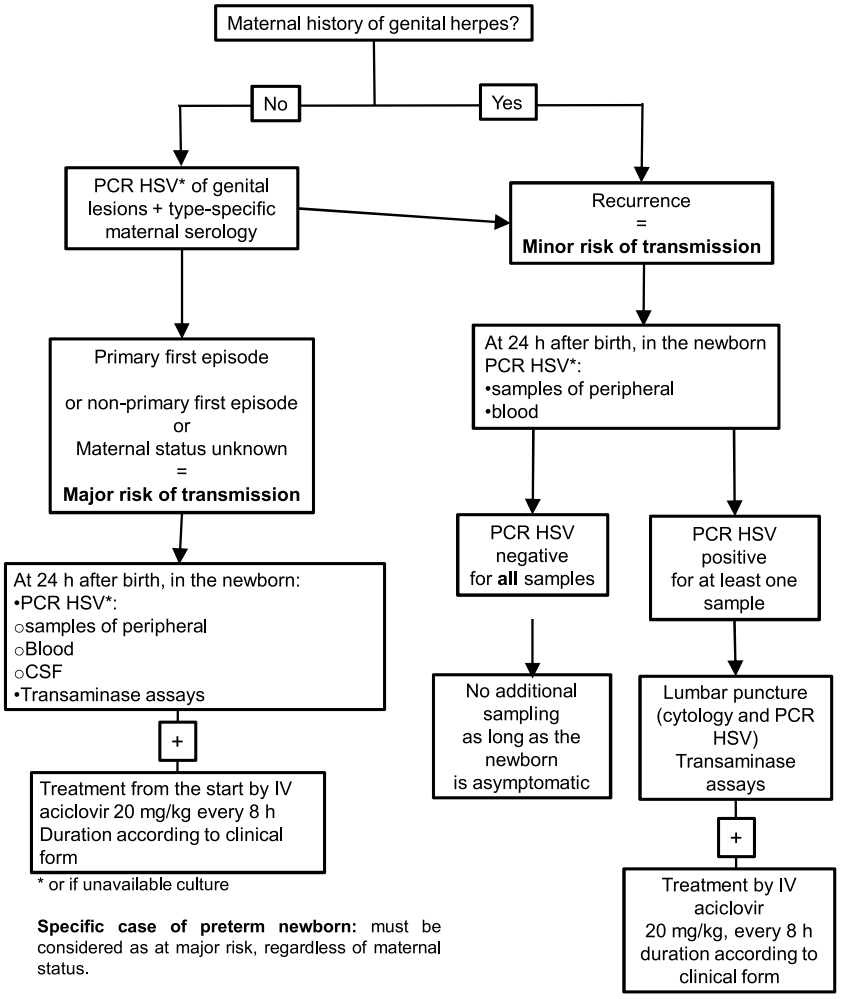

Fig. 5. Management of an asymptomatic newborn born by vaginal or cesarean delivery to a mother with an active genital herpes lesion. Adapted from Kimberlin et al. [17].

end of the first week of life, transaminase assays can be performed for newborns with an infection or neurological signs to assess potential liver effects (professional consensus), which could be evidence of herpes infection. Normal transaminase levels, however, do not rule out neonatal herpes (expert opinion).

When CNS effects are suspected, complementary examinations (electroencephalogram and cerebral magnetic resonance imaging) can be performed to obtain evidence of the diagnosis (professional consensus).

Virologic confirmation of the diagnosis is based on PCR (professional consensus):

- Every newborn with suspected neonatal herpes must have a lumbar puncture for CSF for PCR to test for HSV (professional consensus).
- To improve the probability of diagnosis, multiple samples must be taken and performed as early as possible, preferably before treatment but without delaying it (professional consensus).
- When the PCR is negative for HSV but clinical suspicion of neonatal herpes is strong, sampling must be repeated and other sites should be included (e.g., mucosa and skin) (professional consensus).

Newborns with suspected neonatal herpes must receive treatment by intravenous aciclovir, without awaiting virologic confirmation (Grade A).

Management of newborns at risk of neonatal herpes depends on the assessment of the risk of mother-child transmission:

- In cases of recurrence (minor risk of transmission), cutaneous and blood samples must be taken for PCR at 24 h after birth (professional consensus). When positive, PCR of the CSF must be performed and curative aciclovir treatment begun (professional consensus).
- When the mother's herpes is a primary first episode or non-primary first episode of genital herpes (major risk of transmission), the cutaneous, blood, and CSF samples for PCR must be taken at 24 h after birth and presumptive aciclovir treatment must begin while awaiting the results (professional consensus).

Intravenous aciclovir at a dosage of 60 mg/kg/day is used to treat neonatal herpes (Grade C).

The treatment duration depends on the specific indication: 14 days for isolated mucocutaneous forms, and 21 days for the disseminated and cerebrospinal forms (professional consensus). A 10-day duration is recommended for "preventive" treatment.

When the disease is identified in an isolated location or associated with the CNS, a lumbar puncture for a CSF sample for PCR is required before treatment ends. If positive, intravenous aciclovir treatment must continue until the PCR results are negative (professional consensus). Follow-up with oral aciclovir at a dose of a dose of 300 mg per square meter of body-surface area, administered three times daily for 6 month is recommended, regardless of the clinical form, to improve the neurological prognosis and reduce the risk of recurrence ("suppressive therapy") (Grade B) (Fig. 5). Postnatal transmission principally concerns HSV-1. Contamination results from direct contacts between the newborn and a herpes lesion (LE4). The risk of transmission via asymptomatic shedding in person with a history of labial herpes is unknown. Maternal breastfeeding is not contraindicated except in cases of a nipple lesion. There are no data about the risk of transmission by breast milk (professional consensus).

Parents, family, and healthcare personnel must know the rules about the prevention of postnatal HSV transmission (professional consensus).

Sponsor

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Appendix A. A1 Steering committee

A1 Steering committee

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