CHRONIC HEPATITIS AND PREGNANCY

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1. HEPATITIS B VIRUS (HBV)

1.1. INTRODUCTION

1.1.1. Epidemiology:

The World Health Organization estimates that in 2019, 296 million people were living with chronic hepatitis B virus (HBV) infection worldwide, and that 820,000 had died from HBV infection, mostly as a result of cirrhosis or hepatocellular carcinoma. Spain is considered a low endemicity country with <1% of chronic HBV infection prevalence. The highest endemicity countries are mainly located in Africa and Asia.

As a result of the implementation of universal hepatitis B immunisation at birth in the '90s, HBV infection prevalence in reproductive age women has significantly dropped. Nowadays, the prevalence of HBV infection in pregnant women in Spain ranges from 0.1% to 4.4%, mostly due to the migrant population from high endemicity areas.

1.1.2. Natural history of HBV infection and clinical manifestations

Hepatitis B can be transmitted by blood, semen, or other body fluids from an infected person through sexual contact, by sharing needles, syringes, or other drug-injection equipment, or by mother-to-child transmission (perinatal or vertical transmission).

The risk for a chronic infection is related to the age at infection: about 90% of infants with hepatitis B will develop chronic infection, whereas only 2%–6% of the people infected from hepatitis B as an adult will become chronically infected.

The natural history of chronic HBV infection has been schematically divided into five phases, taking into account the presence of HBeAg, HBV DNA levels, alanine aminotransferase (ALT) values and the presence or absence of liver inflammation:

1. ***Phase 1: HBeAg-positive chronic HBV INFECTION****, previously termed "immune tolerant"*: HBeAg +, very high levels of HBV DNA, and ALT persistently within the normal range. This phase is more frequent and prolonged in subjects infected perinatally.
2. ***Phase 2: HBeAg-positive chronic HEPATITIS B****, previously termed "immune reactive":* HBeAg+, high levels of HBV DNA and elevated ALT. It may occur after several years of the first phase and is more frequently and/ or rapidly reached in subjects infected during adulthood.
3. **Phase 3: HBeAg-negative chronic HBV INFECTION**, previously termed 'inactive carrier' phase: HBeAg negative, anti-HBe antibodies positive, undetectable or low (<2,000 IU/ml) HBV DNA levels and normal ALT.
4. **Phase 4: HBeAg-negative chronic HEPATITIS B**, HBeAg negative usually with detectable anti-HBe, and persistent or fluctuating, moderate to high levels of serum HBV DNA, as well as fluctuating or persistently elevated ALT values.
5. **Phase 5: HBsAg-negative phase** is characterised by serum negative HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs). This phase is also known as "occult HBV infection". Patients in this phase have normal ALT values and usually, but not always,

undetectable serum HBV DNA. Immunosuppression may lead to HBV reactivation in these patients.

In most cases of chronic HBV infection, there are no clinical manifestations. Sometimes nonspecific symptoms may appear, such as fatigue or discomfort in the right hypochondrium. In cases of advanced liver disease or cirrhosis, which are rare in the pregnant population, a constitutional syndrome, jaundice, or stigmata of chronic liver disease (spider veins, palmar erythema, hepatosplenomegaly) may appear. Major complications of cirrhosis (extensive liver damage) include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, variceal bleeding, and hepatorenal syndrome . In rare cases hepatocarcinoma can be diagnosed during pregnancy and it is believed to have a worse prognosis than in non-pregnant women, probably related to the oestrogen elevation and immune suppression in pregnancy.

In case of a reactivation of chronic hepatitis, the clinical manifestations are similar to acute hepatitis. HBV reactivation is characterised by a sudden increase in the level of serum HBV DNA that is most often associated with a moderate to marked elevation of serum alanine aminotransferase (ALT) levels. It differs from acute hepatitis because IgM antiHBc is usually negative. In the presence of symptoms compatible with reactivation, superinfection by HDV must also be ruled out.

Due to immunological changes after pregnancy, reactivation is not uncommon in the postpartum period (5-15%) and usually occurs within the first weeks after delivery.

1.2. DIAGNOSIS OF MATERNAL INFECTION

The diagnosis of HBV infection is established through serological testing.

	HBsAg	AntiHBs	AntiHBc	
			IgG	IgM
ACUTE HBV infection	+/-	-	-	+
CHRONIC HBV infection	+	-	+	-
OCCULT HBV infection	-	+/-	+	-
SOLVED HBV infection	-	+	+	-
VACCINATED	-	+	-	-

Table 1. Interpretation of HBV serologic test results.

Chronic infection is considered as HbsAg+ persisting for more than six months (after their first blood test result).

1.2.1. Evaluation of the phase of infection

To properly assess the activity and the phase of the infection, the following should be determined at the first antenatal assessment:

- **Quantitative DNA of HBV and HBeAg**

Quantification of DNA should be determined in all cases as it is the most sensitive method to evaluate viral replication. HBeAg will also be requested.

The quantitative determination of the surface antigen or HBsAg (qHBsAg) is another useful marker to distinguish an "inactive Carrier" from a HbeAg-chronic hepatitis B". Low values (<1000 IU/mL) suggest that it is a chronic infection in the HBeAg-negative chronic HBV infection phase. This marker is also useful for hepatologists to monitor patients during antiviral treatment once they have undetectable viral load as it correlates with the degree of intrahepatic replication of HBV.

- **Basic biochemistry and liver profile with transaminases. Coagulation test**.
  To evaluate cytolysis and liver function.

1.2.2. Screening for maternal HBV infection in pregnancy

Universal HBV screening for all pregnant women is recommended in order to identify the best management strategy for mothers and the correct immunoprophylaxis schedule for future newborns to prevent vertical transmission. Ideally, it should be performed at the first trimester of pregnancy. Results from HBV serology should always be available before delivery.

In a patient with risk factors (risk profession, sexual promiscuity, intravenous drug users (IVDU), domestic or sexual contacts with HBV carriers, haemodialysis, recipients of blood products, with HIV infection, chronic liver disease, and international travellers), vaccination is recommended starting in the 2nd trimester after confirming the absence of immunity (AntiHBc and AntiHBs negative), according to the specific "Vaccines and Pregnancy" protocol. In a patient with risk factors who has not been vaccinated, serology should be repeated in the 3rd trimester.

1.3. RISK FACTORS FOR VERTICAL TRANSMISSION (VT) OF HBV

Vertical transmission of HBV occurs primarily during labour and delivery, through exposure to cervicovaginal secretions and maternal blood.

There may also be intrauterine transmission through placental leakages or contact with maternal blood in case of invasive procedures (especially in cases with high viral load or HBeAg positive). The risk of vertical transmission of HBV depends on the HBeAg status and viral load (HBV DNA). Without any preventive measures, the risk of vertical transmission for hepatitis B e antigen (HBeAg) positive mothers, ranges from 70% to 90% and from 10% to 40% for HBeAg negative mothers. In addition, it should be noted that up to 80%-95% of infected newborns will develop a chronic infection.

1.4. PREGNANCY MANAGEMENT IN HBV INFECTED PREGNANT WOMEN

- Upon diagnosis of HBV infection, the patient should be referred to the Perinatal Infection Unit for the specific management of pregnancy together with the Viral Hepatitis Unit.
- A complete HBV activity profile should be requested at the first appointment (HBeAg, quantitative HBV DNA, transaminases, coagulation) for proper assessment of the activity and phase of the infection. In all cases (regardless of DNA levels), the patient should be referred to the hepatology service for treatment evaluation and subsequent follow-up.
- It is recommended to re-evaluate the activity profile at the time of the 2nd trimester analysis (24-26

weeks of gestation), in all patients, even if undetectable DNA and negative HBeAg previously.

- It is recommended to perform standardised endocervical and vaginal cultures to rule out concomitant sexually-transmitted infections that may increase the risk of vertical transmission (VT) at around 30 weeks of gestation,.
- HCV serology should be requested.
- It is advisable to refer the patient's partner to the reference GP or Sexual Health Centre for serological evaluation and potential vaccination if not immunised.
- Recommend serological control of the patient's previous children by the reference GP/paediatrician (especially if previous births in other countries). Recommend complete vaccination in non-infected children without protective vaccine antibody titers.
- Acute hepatitis B infection is associated with an increased incidence of preterm birth and low birth weight, and the risk of vertical transmission is higher (up to 60% if it occurs in the third trimester). Treatment of acute hepatitis B requires management by a hepatologist, with supportive treatment and close monitoring of liver function. In cases of acute liver failure or severe hepatitis, antiviral treatment may be necessary.
- Whenever possible, it is recommended to request an assessment with the paediatric infectious diseases service in the third trimester for advice and postnatal follow-up.

1.4.1. Antiviral treatment in pregnancy

- Regardless of pregnancy, hepatitis B infection may require antiviral treatment for management. Indications for antiviral treatment outside of pregnancy can be found in local or international guidelines for the management of chronic hepatitis B infection (active chronic hepatitis, with liver or extrahepatic complications, at risk of reactivation due to immunosuppressive treatment, etc.).

- Antiviral treatment may also be indicated during pregnancy, not for maternal indication, but only to prevent vertical transmission (see section 1.5.2)

  If a woman is receiving antiviral treatment during pregnancy, it is recommended to keep her under treatment, modifying the regime to the safest drugs in pregnancy according to the current evidence (lamivudine, tenofovir, telbivudine). Tenofovir disoproxil fumarate is currently the drug of choice during pregnancy according to most of the international guidelines (Category B of the FDA) due to its efficacy and low rate of resistance. Tenofovir alafenamide is not currently recommended for use during pregnancy as there is insufficient evidence of its safety in pregnancy. Telbivudine (Category B of the FDA) or lamivudine (Category C of the FDA) would be other therapeutic alternatives.

1.5. PREVENTION OF VERTICAL TRANSMISSION

1.5.1. Passive-active prophylaxis

The most effective strategy to prevent vertical transmission of HBV is neonatal passive-active immunisation, consisting of:

- Administration of specific immunoglobulin against HBV (HBIG): 100 IU (0.5 ml) before 12

hours of life.

- HBV vaccine with administration of first dose before 12 hours of life.

All 3 doses of the vaccine must be completed, adapted to the systematic vaccination schedule (0-1-6 months).

These postnatal prophylaxis must always be applied in all newborns from pregnant women with confirmed HBV infection regardless of whether they have received antiviral treatment during pregnancy, and in pregnant women with unknown serological status. The efficacy of these measures is 85 -95%. Prophylaxis failures may be due to:

- Intrauterine transmission (higher risk if HBeAg + or elevated HBV DNA)
- Non-compliance with HBIG + vaccine guidelines
- Failure to generate HBsAc antibodies

Most cases reported with failure in the prevention of VT after prophylaxis with HBIG and vaccine had HBeAg + and/or viral load> 200,000 IU/.

1.5.2. Antiviral treatment in pregnancy

In order to reduce the number of postnatal prophylaxis failures, which mainly occur in HBeAg+ patients and/or high viral load, it is recommended to start antiviral treatment during pregnancy in the following cases:

- HBV DNA > 200,000 IU/ml (or > 1,000,000 copies/ml).
- Women with lower levels of HBV DNA but with a history of vertical transmission in previous pregnancies.
- Maternal indication for treatment (following recommendations in section 1.4.1).

Treatment is generally started between 24-28 weeks of pregnancy. Tenofovir is the drug of choice during pregnancy, as mentioned in section 1.4.1, due to its safety profile, potent antiviral activity, and high genetic barrier. It is recommended to prolong it for a few weeks (4 to 12 weeks) after delivery to avoid reactivation. The suspension of the drug will be evaluated by hepatology in the postpartum follow-up.

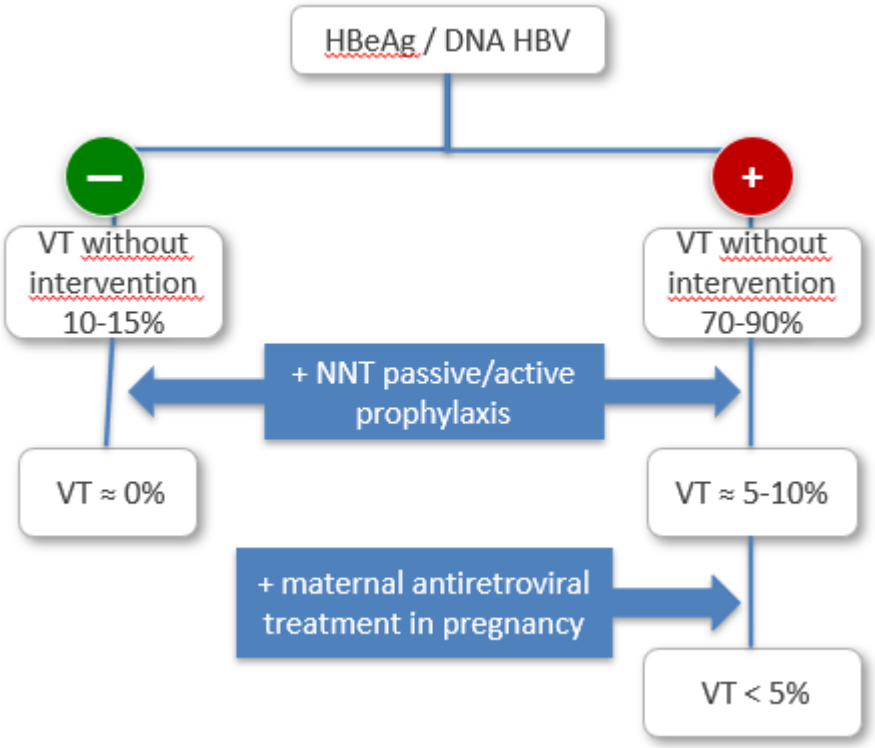

Figure 1. Vertical transmission of HBV according to viral activity and prevention strategy.

1.5.3. Prenatal diagnosis / Invasive procedures

To screen for chromosomal abnormalities in pregnant women with HBV infection, the best available non-invasive test will be performed according to gestational age. In high-risk cases, the risks and benefits of performing an invasive test should be discussed.

The invasive procedure of choice for prenatal diagnosis will be an amniocentesis. There is scarce information regarding HBV transmission and chorionic villous sampling (CVS). As it may have a higher theoretical risk of transmission, a CVS would not be recommended.

Globally, the risk of vertical transmission of HBV associated with amniocentesis is low, but appears to be increased in the case of HBeAg or positive DNA. The following recommendations should be followed:

- An invasive procedure should not be performed without a serological result (HBsAg, HIV, HCV).
- The degree of infection activity must be available prior to the procedure (HBeAg, quantitative HBV DNA, transaminases).
- Avoid transplacental amniocentesis. If not possible, delay the procedure.

Post-procedure prophylaxis with HBIG: Administration of specific HBV immunoglobulin post-procedure (600 IU single dose within 24 hours) is recommended in cases with positive HBeAg or detectable HBV DNA, in cases where transplacental amniocentesis cannot be avoided, in amniocentesis performed in

the 3rd trimester or when, after a detailed risk-benefit assessment, invasive procedures of higher theoretical risk of transmission are performed: CVS, cordocentesis, amniodrainage, fetal surgery.

In cases of cervical incompetence, threatened preterm labour, or preterm rupture of membranes (PROM), the risk-benefit of diagnostic amniocentesis for assessment of intra-amniotic infection should be carefully discussed/evaluated. It may be limited to cases with clinical suspicion of intra -amniotic infection.

1.5.4. Intrapartum management

- If there is no activity profile in the 3rd trimester, request HBeAg and quantitative HBV DNA at admission.
- Mode of delivery: based on current scientific evidence, caesarean delivery does not seem to protect against HBV transmission. HBV infection will therefore not modify the mode of delivery.
- Avoid invasive intrapartum procedures (invasive fetal heart rate monitoring, intrapartum fetal blood sample), which are formally contraindicated in cases of infection with positive HBeAg or detectable HBV DNA. Nor is their use recommended in cases with negative HBeAg and undetectable HBV DNA, but the decision could be customised taking into account the risks and benefits.

1.5.5. Breastfeeding

Despite the presence of hepatitis B virus (HBV) in breast milk, there is no evidence of a higher risk of vertical transmission in cases of breastfeeding compared to artificial feeding, as long as passive-active immunisation guidelines are properly applied. Therefore, hepatitis B infection does not contraindicate breastfeeding in infants who are given HBIG at birth in combination with the complete vaccination schedule. Likewise, in mothers treated with Tenofovir, the treatment does not need to be discontinued. Although data on the use of tenofovir during breastfeeding are scarce, the breast milk concentrations of the drug are very low and, given its very limited oral bioavailability, the infant's exposure is minimal.

1.6. POSTPARTUM

- Maternal-fetal Medicine Follow-up at 6 weeks after delivery (Perinatal Infections Unit) to ensure that follow-up circuits are active for both the mother and the newborn.
- Hepatologist Follow-up: Due to the immune and hormonal changes after pregnancy, there is an increased risk of hepatitis B reactivation in the first postpartum months. In cases treated with antivirals, the patient must continue the treatment until indicated by the reference hepatologist. If an antiviral treatment was initially indicated, it will be continued according to clinical guidelines. If an antiviral treatment was started only for the prevention of vertical transmission (for example, in immunotolerant patients), it will be maintained for at least 3 months after delivery and the patient

will be followed during the first year to detect potential reactivation episodes.

1.7. POSTNATAL FOLLOW-UP

All cases, including those with negative HBV DNA, must have follow up in the Paediatric Infectious Diseases Unit, to ensure proper vaccination and subsequent serological evaluation.

In the case of mothers treated with antivirals or with positive DNA and high viral load, it is recommended to determine HBV DNA, HBeAg, and HBsAg 48 hours after birth with subsequent follow-up at the reference Paediatric Infectious Diseases Unit.

At 9 months of age, a blood test with HBsAg and HBsAc will be performed to rule out vertical transmission and to confirm the effectiveness of the vaccine.

1.8. PRECONCEPTIONAL COUNSELLING

Preconceptional counselling may be important for women with some degree of liver insufficiency and when they are receiving antiviral treatment.

If the woman is receiving antiviral treatment, in general it is not recommended to suspend it due to gestational desire or once pregnant. It is recommended to switch to the safest option in pregnancy according to the international guidelines (mainly tenofovir).

In cases of advanced liver insufficiency or liver cirrhosis, pregnancy is not recommended due to the maternal morbidity and mortality associated with pregnancy.

2. HEPATITIS C VIRUS (HCV)

2.1. INTRODUCTION

2.1.1. Epidemiology

Approximately 170 million people are estimated to be infected with hepatitis C virus (HCV) worldwide. The global prevalence in Southern Europe (including Spain, Italy, Greece, and France) ranges from 2.5% to 3.5%.

2.1.2. Transmission and natural history

Hepatitis C can lead to chronic infection in 55-85% of cases. Active infection with increased transaminases develops in 60-70% cases of chronic hepatitis. 20% of chronic infections progress to liver cirrhosis, with an annual incidence of hepatocarcinoma between 1 and 4%. There are different genotypes of HCV; genotypes 1b, 3, and 4 predominate in Europe. The genotype is not correlated with the risk of vertical transmission.

HCV can be transmitted through parenteral routes (transfusion, transplantation, accidental contact with infected blood or needles), sexually (rarely) or vertical transmission. In up to one-third of cases, the transmission mechanism is unknown.

The likelihood of developing a chronic infection in cases acquired perinatally is around 80%.

2.2. DIAGNOSIS OF MATERNAL INFECTION

The determination of anti-HCV antibodies will be the initial screening method for HCV infection. The presence of anti-HCV antibodies may indicate a cured infection or chronic infection. For the diagnosis of chronic infection, the determination of HCV RNA is required:

- Positive: Chronic infection if it persists for more than 6 months.
- Negative: It can be negative in cases of spontaneous resolution (cured acute infection) or in cases treated with interferon + ribavirin, or with the new direct antiviral agents (DAAs). In the latter case, the infection is considered cured if HCV RNA remains negative for 3 or 6 months after treatment has been completed.

In case of suspicion of recent acute contact, anti-HCV antibodies may be negative (seroconversion period or detection interval). In these cases it is recommended to request HCV RNA or a new follow-up in 3-6 months.

In case of chronic HCV infection, it is recommended to evaluate the liver disease stage through a Transient Elastography (Fibroscan) and a liver ultrasound. Both procedures can be performed during or after pregnancy, although it should not be delayed if advanced liver disease is suspected.

2.2.1. Screening for HCV infection in pregnancy

HCV Screening should be performed on all pregnant women with known risk factors:

- History of drug use.
- History of transfusion or previous organ transplant, especially before 1992.
- HIV or HBV infection.
- Partner infected with HCV.
- Chronic hypertransaminasaemia.
- Tattoo wearer.
- Piercings made with non-sterile or single-use material.

In pregnant women with follow-up in our centre, given the availability of postpartum treatment that can improve maternal prognosis and prevent the risk of vertical transmission in subsequent pregnancies, screening will be recommended for all pregnant women even if they do not have risk factors. In women without risk factors who come directly to our centre for delivery assistance and have not been previously screened, HCV determination will not be systematic.

2.3. RISK OF VERTICAL TRANSMISSION

The overall risk of vertical transmission of HCV in pregnant women with anti-HCV antibodies is very low, below 1.7%. In pregnant women with HIV coinfection, HCV transmission increases to 15-20%. Transmission occurs mainly in the peripartum period.
The known risk factors for HCV vertical transmission are:

- Positive HCV RNA. When HCV RNA is positive, vertical transmission occurs in 4 -5% of cases. Although many authors have described a higher risk with a higher viral load, there are still controversial data on this matter. There is no defined viral load cut-off below which there is no risk of vertical transmission.
- Prolonged premature rupture of membranes.
- Intrapartum invasive procedures that increase exposure to maternal blood: invasive fetal monitoring, intrapartum fetal blood sampling.
- HIV coinfection

2.4. PREGNANCY MANAGEMENT IN THE PREGNANT WOMAN INFECTED WITH HCV

Upon diagnosis of HCV infection, refer the patient to the Perinatal Infections Unit for specific management of pregnancy and to the Viral Hepatitis Unit to assess the extent of liver disease and consider starting antiviral treatment after the pregnancy and breastfeeding period.

-Request a full HCV activity profile (quantitative HCV RNA, transaminases, coagulation) at the first appointment to properly assess activity and the phase of infection.
-It is recommended to evaluate the stage of the disease through a transient elastography (Fibroscan) and a

liver ultrasound. Both procedures can be performed once the pregnant woman has given birth, although in the case of suspicion of advanced liver disease it is essential to perform them immediately.

- Revaluation of the activity profile in the third trimester.

- Perform standardised endocervical and vaginal cultures to exclude concomitant sexually-transmitted diseases that may increase the risk of vertical transmission.

- If HBsAg is negative and not immunised, vaccination against HBV (from the second trimester) to prevent HBV coinfection is recommended, as coinfection increases the risk of progression of liver disease.
Whenever possible, it is recommended to refer to the Paediatrics Infectious Diseases Unit in the third trimester for counselling and postnatal follow up.

2.4.1. Influence of maternal HCV during pregnancy:

During the second and third trimesters of pregnancy, transaminase levels tend to decrease. After delivery, an increase in the same is common. The evolution of the viral load tends to be the opposite; it increases in the second and third trimesters, and significantly decreases after delivery.

As for the risk of perinatal complications, an association with different adverse perinatal outcomes (gestational diabetes, preeclampsia, intrauterine growth restriction, antepartum bleeding, and premature birth) has been described, although in many cases this association may be affected by the existence of confounding factors. Fetal growth monitoring would be indicated as a high-risk pregnancy.

The incidence of gestational cholestasis is increased in pregnant women with chronic HCV infection, reaching up to 20%. The clinical presentation may be earlier or more severe.

2.4.2. Treatment during pregnancy:

Based on the available data, treatment of chronic HCV infection is not recommended during pregnancy.

The preferred drugs for chronic HCV infection are direct-acting antiviral agents (DAAs). These are drugs that directly attack the main targets of the virus (protease inhibitors, polymerase inhibitors, and NS5A inhibitors). They are administered orally, usually for 8-12 weeks. There is no data on the safety of the drug during pregnancy, so its use is not recommended during pregnancy and breastfeeding. However, studies in animals with sofosbuvir and ledipasvir (SOF/LDV) have not shown teratogenicity, being classified as category B by the FDA. A clinical trial is currently in progress to establish the safety of using DAAs in pregnant women in the second-third trimester of pregnancy. In the event that a woman becomes pregnant while receiving treatment, an individual assessment of the risk/benefit of continuing antiviral treatment or suspending it based on the degree of hepatopathy, gestational age, and week of antiviral treatment should be performed. The decision will be made by the patient, the Maternal-Fetal Medicine team, and the Hepatology team, in agreement.

Postpartum treatment is recommended, once breastfeeding has stopped, for any woman of childbearing age with chronic HCV infection, to prevent vertical transmission in subsequent pregnancies.

Ribavirin, although currently indicated in very selected cases (e.g. patients with decompensated cirrhosis), is a known teratogenic drug (FDA X classification) that should be discontinued 4 -6 months before pregnancy, due to its high half-life. In the event of pregnancy under treatment with Ribavirin, a legal termination of pregnancy may be considered justified. Peginterferon is no longer used as treatment for chronic HCV infection due to its low efficacy and high rate of side effects.

	FDA	Teratogenicity	Recommendations
DAAs		Unknown in humans. All except Viekirax (minimally) cross the placenta	Avoid during conception and pregnancy. Contraindicated during breastfeeding.
Sofosbuvir/ledipasvir	B	Not in animals	
Dasabuvir	B	Not in animals	
Ledipasvir	B	Not in animals	
Daclatasvir		Not in animals	
Viekirax	B	Not in animals	
Simeprevir	C	Not in animals	
Peginterferon alfa-2a	C	Increased risk of abortion	Avoid during conception and pregnancy. Very low risk during breastfeeding.
Ribavirin	X	Teratogenic (craniofacial, skeletal, and gastrointestinal malformations), mutagenic, and carcinogenic in animals.	♀: Avoid pregnancy during treatment and for 4 months after stopping treatment ♂: Avoid conception during treatment and for 6-7 months after stopping treatment

			Low risk during breastfeeding

Table 2. Teratogenicity of drugs for the treatment of HCV.

2.5. PREVENTION OF VERTICAL TRANSMISSION

2.5.1. Prenatal diagnosis / Invasive procedures

To screen for chromosomal abnormalities in pregnant women with HBV infection, the best available non-invasive test will be performed according to gestational age. In high-risk cases, the risks and benefits of performing an invasive test should be discussed. There is very limited information on the potential for HCV transmission via amniocentesis and there is no information on the risk of vertical transmission through other invasive procedures.

The following recommendations should be followed:

-The invasive procedure of choice for prenatal diagnosis will be amniocentesis. There is no information on the vertical transmission of HCV by a chorionic villous sampling. Due to the higher theoretical risk of transmission due to greater maternal-fetal blood contact, its application is not recommended in cases of HCV infection.
- An invasive procedure should not be performed without a serological result (HBsAg, HIV, HCV).
- If possible, request HCV RNA before the procedure.
- Avoid transplacentary procedures. If this is not possible, delay the procedure.
- In cases of cervical insufficiency, threatened preterm labour, or preterm rupture of membranes (PROM), the risk-benefit balance of diagnostic amniocentesis for assessment of intra-amniotic infection should be carefully discussed/evaluated. It may be limited to cases with clinical suspicion of intra-amniotic infection.

2.5.2. Intrapartum care

2.5.2.1. *Pregnant women with negative 3rd trimester HCV RNA:* If the RNA is negative in the third trimester, the risk of vertical transmission is negligible, so the obstetrical management will be similar to that of a non-infected woman.

2.5.2.2. *Pregnant women with positive or unknown 3rd trimester HCV RNA*

- If the HCV RNA is unknown, quantitative HCV RNA should be determined at admission and consider urgent processing if needed for clinical decisions.
- Mode of delivery: based on current scientific evidence, the mode of delivery does not affect the risk of vertical transmission of HCV. In cases of co-infection with HIV, it has not been shown that elective caesarean delivery is protective against HCV vertical transmission.
- Avoid prolonged premature rupture of membranes.
    - At term: An active management with an immediate induction of labour is recommended. Expectant management is not recommended and ideally induction of labour should start before 6 hours of PROM.
    - Preterm:
        - Determine RNA HCV with urgent processing in all cases of PROM to facilitate management if the RNA is negative.
        - Assess the risk-benefit balance of diagnostic amniocentesis. It may be limited to cases with clinical suspicion of intra-amniotic infection. If performed, a transplacentary procedure should be avoid as much as possible.

- Decision-making based on gestational age
  - ≥ 35.0 weeks: Active management with immediate induction of labour, ideally starting the induction of labour before 6 hours of PROM.
  - < 34.6 weeks: Based on the available scientific evidence, the risk - benefit between the morbidity and mortality associated with prematurity and the possibility of an increased risk of vertical transmission do not justify ending the pregnancy for this reason. The current PROM protocol will be followed.
- Avoid invasive intrapartum procedures (invasive fetal heart rate monitoring, intrapartum fetal blood sampling)

2.5.3. Breastfeeding

Despite the presence of VHC RNA in breast milk, breastfeeding does not increase the risk of perinatal transmission of VHC. Nipple injuries that may cause bleeding during feedings should be avoided. The use of AADs during breastfeeding is not generally recommended.

2.6. POSTPARTUM

Maternal-fetal Medicine Follow-up at 6 weeks after delivery (Perinatal Infections Unit) to ensure that follow-up circuits are active for both the mother and the newborn.

In cases with positive VHC RNA, referral to Hepatology will be made to consider treatment with AADs once breastfeeding period completed.

2.7. POSTNATAL FOLLOW-UP

All babies born to mothers with positive HCV will be referred to the reference Paediatric Infections Unit for follow-up.

To confirm vertical transmission:

- Positive HCV RNA repeated on 2 occasions separated by 3-6 months.
- Positive anti-HCV antibodies at 18 months old.

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