Editorial Commentary

Viral hepatitis management in pregnancy: practical insights from a pediatric perspective

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The American College of Obstetricians and Gynecologists (ACOG) recently published a Clinical Practice Guideline that focuses on the management of viral hepatitis before, during, and after pregnancy (1). These recommendations encompass critical aspects of care for pregnant or postpartum people who test positive for viral hepatitis infections, primarily including hepatitis B virus (HBV) and hepatitis C virus (HCV). In this commentary, we will explore these recommendations from a pediatric viewpoint, emphasizing their significance for the health and well-being of children born to mothers with viral hepatitis.

Vertical transmission: a key concern

One of the primary considerations in managing viral hepatitis before and during pregnancy is the potential to reduce the risk of vertical transmission, which is the primary mode of infection in children worldwide (2-4) and can lead to chronic infections, resulting in significant long-term morbidity and mortality. Adhering to recommended screening and to pre-pregnancy, antepartum, intrapartum, and postpartum management strategies (summarized in *Table 1*) (1), healthcare providers can substantially reduce the risk of transmission, leading to better outcomes for these children.

Management before pregnancy

Screening before pregnancy for chronic viral infections is crucial for the possible initiation of appropriate anti-viral treatment. However, while infectious screening is routinely provided during pregnancy, pre-pregnancy screening is often more challenging: chronic viral hepatitis are rarely tested and healthy women of reproductive age do not often present for viral hepatitis screening.

ACOG recommends universal HCV/HBV screening during each pregnancy. Screening during pregnancy is anyhow important as it allows obstetrician-gynecologists to connect the mothers with hepatitis care so that they may begin direct-acting antivirals (DAAs) postpartum and after completion of breastfeeding. For both hepatitis B and C, given the typical absence of sign and symptoms of the infected children (5,6), the appropriate follow-up could only be started if the risk of transmission is correctly evaluated. Universal screening in pregnancy allows for accurate identification of HCV/HBV exposure and thus perinatal transmission risk. However, new HBV or HCV acquisition late in pregnancy would result in a negative screening test earlier in pregnancy and perinatal transmission. Thus, those with identifiable risk factors in pregnancy should be re-screened at delivery. Children with unknown birth exposure

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Table 1 Summary of strategies to prevent vertical transmission of HBV and HCV infection in before pregnancy, during pregnancy, at birth and during the child's first year of life

Virus	Before pregnancy	During pregnancy	At birth	First year of life
HBV	Screening	Screening; anti-viral treatment during the last trimester in highly viremic (>2×10^5 U/mL), HBeAg-positive pregnant people	Anti-HBV vaccine and immunoglobulin within 12 hours of birth in newborns of HBsAg-positive individuals or whose status is unknown	Completion of anti-HBV vaccine schedule (at least 2 more doses within 6–12 months)
HCV	Screening; anti-viral treatment with DAA	Screening; limited data on DAA use; future research is needed	None	None

HBV, hepatitis B virus; HCV, hepatitis C virus; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; DAA, direct-acting antiviral.

status, should be screened for HBV and HCV as well.

HBV

Assessment of maternal HBV status by the means of hepatitis B surface antigen (HBsAg) testing or the triple panel screening (HBsAg, antibody to HBsAg—anti-HBs, and antibody to hepatitis B core antigen—anti-HBc) both before and during pregnancy are crucial to implement the two major strategies to prevent vertical transmission, that are treatment of highly viremic mothers during pregnancy and active and passive immunoprophylaxis at birth for children (2). ACOG recommends early universal prenatal screening for HBsAg of all pregnant people in each pregnancy, regardless of previous testing or vaccination schedule. Triple panel screening is recommended for pregnant patients who do not have a documented negative triple screen result after 18 years of age or who have not completed HBV vaccine series, or in patients with ongoing risks factors for HBV infection, regardless of vaccination status or history of testing.

HCV

Screening of individuals of childbearing age or pre-pregnancy is crucial to provide the opportunity to start a short course of DAAs drugs treatment to clear the infection before the possible pregnancy, thus avoiding vertical transmission. Indeed, at the moment DAAs are not approved during pregnancy and no effective intervention to reduce the risk of transmission could be implemented during pregnancy.

Hepatitis B transmission: the importance of immunoprophylaxis

Without any preventive measures, the risk of vertical transmission of HBV is significant, particularly from highly viremic mothers (about 70–90% for children born from for HBsAg and hepatitis B envelope antigen—HBeAg positive mothers; about 10–40% for children born from HBsAg positive and HBeAg negative mothers) (2). Hepatitis B vaccination within 12 hours of birth, followed by two additional vaccine doses within 6–12 months, is highly (90–95%) effective in preventing infection. In addition, the administration of hepatitis B immune globulin at birth lowers the risk of vertical transmission to less than 5%. While this approach has proven successful in the majority of vaccinated children, breakthrough infections are possible, often due to transplacental or immunoprophylaxis regimen failure (2).

In both high burden-low resource and low burden-high income countries, the birth vaccination dose and the use of immunoglobulins at birth for HBV have not been consistently implemented. This is a crucial point to emphasize from a pediatric perspective, as timely vaccination and immunoglobulin administration can be highly effective in preventing vertical HBV transmission. According to World Health Organization (WHO) data, in 2022 coverage of three vaccine doses was 84% worldwide, while in 2000 it was around 30%. Notably, coverage of the vaccine birth dose is still highly variable: indeed, in 2022 it was 45% worldwide and 18% in the WHO African Region (7).

In a recent survey involving 76 European centers with delivery, maternal screening (HBsAg) was performed in the

first and in the third trimester of pregnancy in 53% and in 46% of the hospitals, respectively. Only 38% of the HBeAg positive pregnant people with elevated viremia received anti-viral treatment during the last trimester of pregnancy. At birth, the vast majority (91%) of the centers administer hepatitis B vaccine to newborns of HBsAg-positive mothers within 12 hours of birth, with great variation in the timing of the hepatitis B vaccine schedule (8).

Ensuring that these interventions are accessible and widely adopted is essential to protect infants from transmission and strategies for global control of HBV infection.

Vertical transmission of hepatitis C and the need for antiviral treatment

Vertical transmission of HCV from mothers who are HCV ribonucleic acid (RNA)-positive occurs in around 6% of cases (3). The risk is higher when the mother is co-infected with human immunodeficiency virus (up to 10%) (9). Maternal viremia is the main risk factor for vertical transmission. Few studies showed an association between higher levels of maternal HCV RNA and a higher risk of vertical transmission, although overlaps of viremia concentrations between transmitting and non-transmitting pregnant people has been reported (3).

According to ACOG guidelines, the risk of vertical transmission of HCV associated with amniocentesis and chorionic villous sampling is generally low. Therefore, shared decision making should be used when counseling patients on the procedures. Although some reports describe an increased rate of perinatal transmission in case of neonatal contact with infected vaginal blood and secretions during delivery, there is insufficient evidence to recommend that invasive obstetric procedures should be routinely avoided and to perform prelabor cesarean delivery (1).

The double benefit of treating hepatitis during pregnancy

Addressing viral infections during pregnancy provides a dual benefit by enhancing the mother's health and minimizing the risk of infection in the child. The treatment of highly viremic HBV-infected mothers during pregnancy is well-established and acknowledged in the ACOG guideline (1). There is growing evidence supporting the treatment of HCV-infected mothers, with the introduction of DAAs showing promise in achieving maternal cure and preventing vertical transmission.

Currently, no approved treatment options exist for hepatitis C virus infection during pregnancy. DAAs offer a potential treatment for mothers with HCV, although further research is needed to establish their safety for pregnant people. While no large randomized clinical trials or prospective cohort studies focusing on DAAs in pregnancy have been concluded, existing data suggest that DAAs do not cause significant modifications in pharmacokinetics (PK) and pose no serious safety issues for HCV-infected pregnant individuals. A pivotal DAA PK study in pregnancy explored the use of the non-pangenotypic sofosbuvir/ledipasvir regimen in nine pregnant women, of whom eight were included in PK analysis. All the patients received the treatment in the second/third trimester, achieved HCV cure with no vertical transmissions or safety concerns (10). Recently, PK of the pangenotypic regimen sofosbuvir/velpatasvir was assessed in 10 pregnant women, with no difference in exposure compared to non-pregnant women and infection clearance in all 10 participants (11).

A 2021 study described a cohort of 100 HCV-infected Egyptian women, who had a negative pregnancy test before the start of DAA and experienced unintended pregnancy during HCV treatment. The women received a 12-week regimen of DAA, with the majority treated with sofosbuvir plus daclatasvir. Nine pregnant people completed the full DAA course against medical advice: seven delivered normal babies, while the remaining two were lost to follow-up. All the women had a sustained virological response (SVR), without any major adverse events reported in both women who stopped or continued treatment (12). Yattoo *et al.* reported 15 HCV positive, non-cirrhotic, pregnant Indian women who received sofosbuvir/ledipasvir during their second-early third trimesters to complete a 12-week course of therapy. SVR was achieved by all women without safety issues, and newborns were delivered without any adverse events (13).

An international DAA pregnancy exposure register has been established, the Treatment in Pregnancy for Hepatitis C (TiP-HepC Registry, NCT05368974). This registry is collecting data on pregnant people living with HCV exposed to DAAs during pregnancy. It aims to scale efforts for HCV screening and therapy during pregnancy, and share pregnancy outcomes. This registry encourages networking and gathers more data for safe DAA treatments. In addition, the registry has the potential to capture safety of first trimester exposures that would not be available in prospective clinical trials.

DAAs are expected to provide high rates of maternal HCV cure by delivery, preventing vertical transmission, primarily occurring in the third trimester. The main risk is the unknown safety of DAAs in pregnancy. Notably, use of DAAs in the late second and early third trimester would essentially eliminate teratogenic effect as organogenesis is complete by 16-week gestation. DAA use in pregnancy represents an opportunity to intervene and significantly reduce the risk of vertical transmission. Therefore, the management of HCV during pregnancy should be explored and incorporated into clinical practice to improve outcomes for both mothers and children.

Maternal counseling: what happens to infected children after birth? The natural history of hepatitis B and C in childhood

As acknowledged in the guidelines, pre-pregnancy counseling for people living with HBV or HCV infection includes discussing the risks to the fetus, neonate, and child (1).

HBV infection acquired in infancy and early childhood often leads to chronic hepatitis, with age being a crucial factor in determining the risk of chronicity. Chronic HBV infection develops in 90% of infected newborns and infants but in less than 5% of individuals who acquire the infection in adulthood. Pediatric infections are typically asymptomatic; however, cirrhosis and hepatocellular carcinoma (HCC) are possible rare complications of chronic hepatitis B in pediatric age (14). The primary characteristic of perinatally or early childhood-acquired HBV infection is a high-replication and low-inflammation phase that can last several decades. As regards infection biomarkers of this phase, it is characterized by detectable HBsAg and HBeAg, high HBV DNA levels, and normal or slightly increased serum aminotransferase concentrations. Cirrhosis has been described in 1–5% of HBeAg-positive children, with risk factors including earlier HBeAg seroconversion (before 3 years of age, consistent with severe hepatic necroinflammation) and a longer duration of the HBeAg-positive chronic hepatitis (or immune-active) phase. The risk of HCC in pediatric age is about 2–5%. Chronic hepatitis B in children has also been associated with extra-hepatic manifestations, notably with renal manifestations (acute kidney injury, nephrotic syndrome, non-nephrotic membranous glomerulonephritis, and end-stage renal disease) (5).

Overall, interferon-based treatments and nucleos(t)ide analogues have been approved for pediatric patients with chronic hepatitis B, each with age-specific limitations. Functional cure, obtaining HBsAg seroclearance, with or without positive anti-HBs, with undetectable HBV viremia and HBeAg after a treatment course is still an ambitious target with the currently available anti-HBV therapies. The actual more realistic treatment goals for children with chronic hepatitis B include sustained on-treatment suppression of HBV replication, associated with normalization of aminotransferases, with or without loss of HBeAg and positive antibody to HBeAg (anti-HBe), and improvement in liver histology. Achieving HBsAg seroclearance and development of anti-HBs occurs in less than 1% of patients using nucleos(t)ide analog treatment and in less than 10% of those undergoing interferon-based therapies (15). Notably, in real-world settings the use of interferon-based therapies is very limited in children, due to the subcutaneous administration route and low tolerability due to the high risk of adverse events.

Following HCV vertical transmission, 25–40% of infected pediatric patients naturally clear the infection within the first 4 years of age (16). However, for those who do not clear the infection spontaneously during this period, chronic infection tends to develop and persist into adulthood (17,18). The progression of HCV liver disease is typically slow during childhood, and severe consequences such as cirrhosis or HCC are very rare in pediatric patients. Chronic HCV infection is often asymptomatic in childhood, making its detection challenging.

The histological evolution of HCV infection in adolescents and children is highly variable. While some individuals may exhibit a normal hepatic histology, cirrhosis has been described in approximately 1–2% of chronically infected adolescents and children (19). Decompensated cirrhosis and a few cases of HCC have also been reported. Notably, advanced liver disease and decompensated cirrhosis have been described in children as young as 3 years old, with cases surfacing as early as 1 year after infection. Although the majority of patients enrolled in pediatric studies with long-term follow-up exhibited normal hepatic histology over two decades of observation (16,18), the prevalence of advanced liver disease has been demonstrated in more than one third of the young adults who acquired the infection in childhood (20). Extrahepatic manifestations of chronic HCV infection are rare (21). DAA therapy stands as the cornerstone for treating chronic HCV infection in children as in adults. With the currently available antiviral therapies, HCV is relatively easily treated, and

Table 2 Antiviral drugs approved for children with chronic hepatitis C virus infection [adapted from Indolfi *et al.* (22)]

Activity	Product	Formulations	Approval
Regimens with pangenotypic activity	Glecaprevir/pibrentasvir (FDC)	Film-coated tablets (FDC) 100/40 mg; coated granules in sachet 50/20 mg	EMA and US FDA >3 years of age
	Sofosbuvir/velpatasvir (FDC)	Film-coated tablets (FDC) 400/100 mg and 200/50 mg; coated granules in sachet 200/50 mg and 150/37.5 mg	EMA and US FDA >3 years of age
	Sofosbuvir/velpatasvir/voxilaprevir (FDC)	Tablet (FDC) 400/100/100 mg	EMA >12 years of age
	Sofosbuvir + daclatasvir	Daclatasvir; film-coated tablets 60 mg	Not approved for use in children by the EMA and US FDA
Regimens with genotype-specific activity	Sofosbuvir/ledipasvir (FDC)	Film-coated tablets (FDC) 400/90 mg and 200/45 mg; coated granules in sachet 200/45 mg and 150/33.75 mg	EMA and US FDA >3 years of age
	Elbasvir/grazoprevir	Film-coated tablets (FDC) 50/100 mg	EMA and US FDA >12 years of age

FDC, fixed-dose combination; EMA, European Medicines Agency; US FDA, United States Food and Drug Administration in children.

nearly all patients achieve elimination. The primary aim of antiviral treatment in pediatric patients with chronic HCV infection is to eradicate HCV RNA, demonstrated by the achievement of an SVR. Different DAA combinations have now been approved for treatment of children as young as 3 years of age (*Table 2*) (22). The efficacy and the safety profile of these drugs in children are excellent (23,24).

The safety of breastfeeding for mothers with HCV and HBV

The guideline correctly emphasizes the safety of breastfeeding for mothers with HCV and HBV.

However, it is concerning that in many healthcare settings, this information is not consistently implemented. Promoting and supporting breastfeeding among mothers with viral hepatitis infections is vital for the overall well-being and development of infants. Healthcare providers should educate mothers and families about the safety of breastfeeding in these contexts.

The importance of vaccination in pregnancy

The guideline underscores the importance of vaccination during pregnancy, particularly for HBV, for those that are nonimmune, and for hepatitis A virus (HAV). This aligns with the growing recognition of the benefits of maternal vaccination for various infectious diseases, including Bordetella pertussis and respiratory syncytial virus. By vaccinating pregnant individuals against HAV, we can not only protect the mother but also confer passive immunity to the newborn, reducing the risk of infection. Infants and young children with HAV infection are usually asymptomatic but play a key role in transmitting the unrecognized infection to others which underscores the importance of primary HAV prevention within families of women of reproductive age.

Conclusions

In conclusion, ACOG's Clinical Practice Guideline for the Management of Viral Hepatitis in Pregnancy provides essential recommendations to safeguard pregnant people and their children from the consequences of viral hepatitis infections. Preventing vertical transmission of HBV and HCV is a crucial step toward achieving the ambitious goal of eradicating these infections by 2030. Although ACOG guidelines are based on the United States context, these recommendations should be adopted worldwide. However, their application could have some barriers in limited resource-settings.

When these recommendations are implemented comprehensively, they have the potential to significantly reduce the burden of chronic hepatitis in children, enhance their overall health and quality of life, and contribute to global efforts to eliminate viral hepatitis. It is imperative that healthcare providers, policymakers, and the global health community collaborate to ensure the widespread

adoption of these guidelines, particularly in regions with a high burden of viral hepatitis. This collective effort will ultimately pave the way for a healthier future for both mothers and their children.

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