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Hepatitis C virus infection in children: How do we prevent it and how do we treat it?

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Abstract

Introduction—Hepatitis C virus (HCV) infection is an important contributor to the worldwide burden of liver-related morbidity and mortality. Mother-to-child transmission of HCV ranges from 6 to 11% in different populations globally, but accurate estimates on the burden of pediatric HCV infection are limited because screening approaches are not consistent.

Areas covered—The advent of new direct-acting antiviral agents that achieve very high rates of sustained virologic response (representing virologic cure) with short (i.e. 8–12 weeks) regimens has revolutionized the field of HCV treatment and led to the development of global elimination goals for HCV transmission and mortality. However, information on their safety during pregnancy and efficacy in preventing mother-to-child transmission is lacking. Currently, there are no approved treatment regimens with these antiviral agents for children younger than 12 years of age.

Expert commentary—If these agents are shown to be safe during pregnancy and effective in preventing transmission to the infant, screening of pregnant women and antenatal treatment of those infected, could pave the way for eliminating pediatric HCV infection-particularly as these drugs become less costly and more accessible. Treatment of infected children when indicated, along with universal safe health care practices, can further pediatric HCV elimination.

Keywords

Children; direct-acting antivirals; Hepatitis C Virus; pregnant women

1. Introduction

Hepatitis C virus (HCV), a small single-stranded RNA flavivirus, is a major contributor to the global burden of liver-related morbidity and mortality, and is responsible for an

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estimated 27% of cirrhosis and 25% of hepatocellular cancer cases [1,2]. Worldwide, an estimated 71 million people are living with HCV infection, and only 20% of individuals are aware of their diagnosis [1,3–6]. The global prevalence of HCV infection varies by region [3]. In terms of absolute numbers, China, Pakistan, India, Egypt and Russia are the five countries with the highest numbers of individuals infected, at over 5 million people each [3]. The global incidence of HCV is estimated at 23.7 per 100,000 persons, with the highest incidence rates found in the African (31.0), and European and Eastern Mediterranean (61.8–62.5) regions [1]. HCV has seven major genotypes (GT) and distinct subtypes, which vary in their geographic distribution and response to therapy [7,8], which has become less of an issue with the advent of new HCV antiviral therapies [1]. Worldwide, GT 1 is the most common (46%), followed by GT 3 (22%), GT 2 (13%) and GT 4 (13%) [7]. Genotypes 1–3 are found globally while genotypes 4, 5, and 6 are most commonly found in northern Africa, South Africa and Asia, respectively [7]. The same distribution has been observed in both children and adults [9].

About 3.5 million people are estimated to be living with HCV infection in the United States (US) [10]. Individuals at risk for HCV infection include those with a history of injection drug use or history of blood or blood product transfusion prior to 1992, hemodialysis patients, children born to HCV-infected mothers and people living with HIV infection [8]. HIV positive individuals have a higher HCV prevalence; injection drug use accounts for the majority of such infections [1].

The most common mode of HCV transmission is through direct exposure to blood such as with injection drug use, parenteral exposure via contaminated medical equipment or transfusion of unscreened blood and blood products [1]. The HCV risk due to using contaminated medical equipment and transfusions in developed countries is inconsequential due to improved medical practices and routine screening of blood and its products whereas in developing countries infections due to transfusion and poor medical practice still occur [1,11]. Other known transmission routes include percutaneous exposure in health care personnel, and sexual transmission [1,12]. The risk of developing HCV infection after percutaneous exposure in occupational settings is low and estimated at 1.9% or less [13]. Sexual transmission of HCV infection is uncommon, although it has occurred in HIV-positive men who have sex with men [14,15]. There is no evidence of transmission through saliva or non-sexual casual transmission [16,17]. Due to the nature of transmission, there is no requirement to exclude children from daycare or schools [18]. Transmission typically does not occur in families but can occur in the presence of direct or inapparent percutaneous or mucosal exposure to blood [18]. In children, 60% of global incident cases of HCV infection are due to mother-to-child transmission, the predominant source of infection in this age category [9,19]. In areas with poor blood screening practices, transfusion-related pediatric infections still pose a challenge [20,21].

In 2016, the World Health Assembly (WHA) approved the Global Health Sector Strategy on Viral Hepatitis, 2016–2021 [22]. For hepatitis C, the 2030 goals of the strategy include targeting a 90% reduction in new cases, a 65% reduction in deaths and treatment of 80% eligible people [1,22]. Five core interventions are outlined: vaccination, prevention of mother-to-child transmission, safe healthcare practices, harm reduction services for people

who inject drugs and testing and treatment [22]. Only the last three interventions pertain to hepatitis C as there are no hepatitis C vaccines or current proven safe and effective approaches for the prevention of mother-to-child HCV transmission. In addition, there is also a dearth of approved treatment interventions for children under 12 years old. As progress is made toward the elimination goals, preventing mother-to-child transmission as well as treating and reducing HCV-related morbidities in children need to remain a key focus.

2. The new landscape of anti-HCV treatment

The latest class of antivirals for the treatment of HCV infection include second- and third-generation direct-acting antivirals (DAAs) [5,23,24]. These DAAs are highly effective and most have not demonstrated fetal harm in animal studies [5,23]. These new agents are categorized in four main groups: protease inhibitors, such as simeprevir, glecaprevir; nucleotide analog polymerase inhibitors, such as sofosbuvir; nonnucleotide analogs, such as dasabuvir and nonstructural (NS5A) protein inhibitors, such as daclatasvir, velpatasvir, pibrentasvir or ledipasvir [24]. These DAAs, when used in combination regimens, result in high rates of sustained virologic response (SVR) representing virologic cure, usually 90% or higher when given in relatively short regimens [5]. These antivirals have revolutionized HCV treatment and are expected to have a major influence on the global epidemiology of HCV infection in the next few years. Some of these newer agents have activity against all HCV genotypes (pangenotypic), which is a significant advantage over the older genotype-specific HCV therapies [1,25].

Despite the favorable profile of the newer DAAs, these agents lack sufficient human pregnancy safety data and are not approved for use during pregnancy. Preclinical and animal data on the safety of Sofosbuvir (SOF) and ledipasvir/sofosbuvir (LDF/SOF) suggest that they may be potential candidates for use during pregnancy. The University of Pittsburgh is currently conducting a phase I clinical trial on the use of LDF/SOF in pregnant women with chronic HCV infection [26]. The results of this trial may lead to options for treatment during pregnancy both for maternal treatment and potentially for prevention of transmission to the infant. Other pangenotypic regimens like sofosbuvir/velpatasvir (Epclusa) [27], the first FDA approved regimen to treat 6 HCV genotypes, need to also be tested in clinical trials during pregnancy, to ensure that treatment options are available regardless of HCV genotype.

3. HCV infection in pregnant women

There is a paucity of data on the prevalence of HCV infection among pregnant women since HCV testing during pregnancy is inconsistent. Although it appears to be similar to that of the general population of childbearing age, it is estimated at approximately 1% [28]. Higher prevalence rates have been reported in some populations; for instance, Egypt has reported a 6% prevalence rate in pregnant women [29]. In the US, HCV incidence is on the rise in women of childbearing age concomitant with the opioid epidemic and increase in injection drug use [30,31].

The impact of acute maternal HCV infection on mother-to-child transmission is not well defined; [23,32] acute infection is considered uncommon during pregnancy and challenging to diagnose without knowledge of the exposure [33]. Pregnancy does not appear to influence the course of HCV infection for the mother [32], although the HCV viral load peaks in the third trimester of gestation [34] while the levels of serum alanine aminotransferase (ALT) decrease during the second and third trimesters [35]. There is conflicting evidence on the relationship between HCV infection and adverse pregnancy outcomes such as preterm delivery [36,37], gestational diabetes, low birth weight, small for gestational age and cholestasis of pregnancy [33].

Approximately 6%–11% of children born to HCV-infected mothers acquire HCV [38]. It is likely that HCV is transmitted both *in utero* and at the time of delivery [39,40]. Based on the timing of detection of HCV RNA by PCR in the infants, the majority of infants are infected perinatally (either late *in utero* or intrapartum) similar to HIV-1 infection [41,42]. Factors that increase perinatal transmission of HCV include fetal monitoring, vaginal lacerations, and prolonged rupture of the membranes (>6 h) [18,33,35,43]. The method of delivery has no effect on transmission risk; thus, caesarean delivery is not recommended as a risk reduction strategy [44]. Breastfeeding is not thought to increase risk of transmission of HCV to the infant as long as the mother's nipples are not cracked or bleeding [35]. When nipples are cracked or bleeding, mothers need to stop breastfeeding, and pump and discard their milk; breastfeeding can be resumed when the nipples have healed [18]. The risk of mother-to-child transmission of HCV is greater in women with HIV coinfection. In the presence of HIV, the transmission rate doubles from 5.8% to 10.8% [38], likely due to an increase in HCV viremia [45,46]. For HIV and HCV co-infected women, HIV suppression with the use of highly active antiretroviral therapy (HAART) may reduce HCV transmission to infants [47].

HCV screening during pregnancy is generally risk-based. The main challenge of risk-based screening is the use of self-report to identify women with risk factors for infection [33] resulting in the possible underestimation of the HCV disease burden among pregnant women and of infant HCV infections acquired perinatally. Broader screening practices could identify cases of previously undiagnosed HCV infection [5,48], as for instance occurred in Italy, where HCV screening is now offered to all pregnant women in the third trimester of pregnancy [49]. Current recommendations by the Centers for Disease Control and Prevention (CDC) and organizations such as the World Health Organization, the American Congress of Obstetricians and Gynecologists (ACOG) and the US Preventive Services Task Force (USPSTF) call for risk-based HCV screening [8,50,51]. However, this practice is shifting. In 2018, the state of Kentucky passed legislation requiring universal HCV testing during pregnancy [52], and the American Association for the Study of Liver Diseases (AASLD) has now recommended universal screening during pregnancy [53]. Until now, universal screening has not been recommended in the U.S. due to the generally believed low prevalence of HCV infection and lack of approved prenatal approaches to prevent mother-to-child transmission [23].

Cost-effectiveness analyses have validated both risk-based [54] and routine HCV screening in pregnant women [55]. With the new screening recommendations and the increased access

to newer antiviral agents, economic analyses on HCV screening should be updated with regard to testing strategies during pregnancy. Furthermore, as more women are screened and potentially diagnosed with HCV infection during pregnancy, the use of DAAs during pregnancy will become an important consideration.

Availability of modalities to prevent transmission of HCV from mother to infant could strengthen the rationale for universal HCV screening during pregnancy. Given that mothers with undetectable HCV viral load rarely transmit to their infants [23], suppressing viremia during pregnancy would be expected to prevent HCV transmission. But, as mentioned, the newer DAA agents lack sufficient safety data for use during pregnancy [5] and pregnancy is currently a contraindication to treatment. Information on the safety of DAAs during pregnancy would have obvious benefits for the pregnant women, as women may become pregnant while on treatment. For some women, pregnancy may represent the main opportunity for clinical care. Such information can be gathered from carefully designed clinical trials as well as from medication registries. Clinical trials are also needed to assess the efficacy of treatment during pregnancy in preventing transmission of HCV to the infant.

4. HCV infection in children

The current global estimate of the number of children under 15 years of age living with chronic HCV infection is 2.1 million [6]. Mother-to-child transmission is the leading cause of pediatric HCV infection and data from Pakistan and Egypt estimate that 25% and up to 50% of HCV cases in children under 5 years of age, respectively, were due to perinatal transmission [56,57]. Pediatric HCV infection is typically asymptomatic and progresses slowly [58,59]. Time between HCV infection and disease development in children is highly variable and severe disease most likely occurs about 2 to 3 decades after infection [9,60]. An estimated 20% of infected children will experience natural clearance of the virus, usually during early infection, by approximately 2.5 years of age; the remainder will develop chronic infection [34,58,61]. As infected children age, the increased severity and progression of liver disease is expected [58]. Children with comorbidities also experience greater liver disease severity [58]. HIV co-infected children experience poorer health outcomes and are less likely to experience spontaneous clearance [61]. This is particularly important for sub-Saharan African countries with higher HIV-HCV coinfection rates [62]. Although the natural history of HCV in children is generally mild, development of liver disease can occur during childhood [59,63]. Extrahepatic manifestations of chronic hepatitis C frequently occurring in adults such as rashes, cryoglobulinemia, glomerulonephritis are less common in children [9]. However, when children present with these conditions, they are prioritized for treatment [53]. Children with HCV also experience reduced health-related quality of life when compared to children without HCV infection. Nydegger et al. demonstrated that children with asymptomatic HCV experienced lowered health scores in most health domains [64]. Rodrigue et al. found that some children may experience cognitive delays and caregivers had high levels of anxiety due to current and future considerations of the infected child’s wellbeing [65]. HCV treatment may be useful in raising quality of life scores and reducing the stress on caregivers; a study examining quality of life in adolescents after HCV treatment found that quality of life scores improved after treatment [66].

Significant costs are associated with the provision of medical care for HCV-infected children in the US, estimated at $17 to $40 million per year [67]. The elimination of pediatric HCV infection is an important goal as pediatric infection is associated with advanced HCV-related conditions in adulthood that lead to morbidity and mortality and furthermore, it poses a huge economic burden. The treatment of pediatric HCV infection should be weighed against the probability of spontaneous clearance considering that children who experience spontaneous HCV clearance will usually do so by the age of two [9].

Pegylated interferon and ribavirin is the only approved HCV treatment regimen for children 3 years and older but its use in routine practice is extremely limited due to adverse effects [68]. For children under the age of 3 years, there are no approved HCV treatment regimens. Recently, in 2017, LDF/SOF was approved as the first direct-acting antiviral for use in children between the ages of 12 and 17 years [69]. This advancement in treatment for pediatric HCV was based on a clinical trial that demonstrated the safety and efficacy of this drug in adolescents with HCV GT 1 infection [70]. Another clinical trial examined treatment efficacy of these drugs in young children (6–11 years old) with primarily HCV GT1 infection, and found cure rates as high as 99% [71,72]. For children with HCV GT4 infection, additional published results on the use of LDF/SOF have also shown high rates of SVR at 12 weeks in a small number of young children (6–12 years old) [73] and in adolescents (12–17 years old) [74]. Yakoot et al. examined the safety and efficacy of sofosbuvir/daclatasvir (SOF/DCV) in 30 adolescent patients and found high rates of SVR at 12 weeks [75]. Several other pediatric HCV clinical trials investigating the safety and efficacy of the DAAs in children as young as 3 are currently ongoing [76]. The 2018 AASLD HCV guidance now has recommendations for using DAAs for the treatment of adolescents and the treatment of all children older than 3 years old, if the DAAs are available for the particular age group [53].

A new era for the treatment of pediatric HCV infection is on the horizon, as there are enormous health and economic rewards to reap by early treatment in this population. Childhood HCV disease affects children, their families and caregivers; and adverse financial and psychological effects can occur [65,77]. The availability of safe and effective treatment options can alleviate this burden. To better understand the need for and benefits of treating pediatric HCV infection, results from the clinical trials will be paramount. Additional research on the economic benefits of childhood treatment, any differences in drug efficacy/response, for instance, tolerability, in adults versus pediatric populations, long-term monitoring for disease recurrence or for drug toxicities, and factors that are associated with early clearance of the virus or disease progression are also necessary.

5. Conclusion

The WHO Global Health Sector Strategy goals, inspired by the availability of new therapies, have revolutionized the approaches to prevent and ultimately eliminate HCV transmission and disease. Treatment of all infected individuals has been proposed as the means to achieve the goals of HCV elimination. Yet, identifying everyone infected with HCV, as well as the cost and availability of the newer therapies, remain major barriers. Estimated costs for a 12 week course of treatment currently range from approximately $150 to $500 in countries with

voluntary licensing agreements for the use of generic DAAs, to $50,000 in some high-income countries [78]. In the US, this has resulted in the prioritization of patients with advanced liver disease and no substance abuse for treatment with DAAs [79]; however, as of now, newer treat-all recommendations are being introduced [53]. DAAs have a special role to play in meeting WHO viral hepatitis goals by 2030 [22]. WHO recommends the prioritization of HCV treatment, including optimizing drug financing mechanisms [1].

6. Expert commentary

Despite the advances in new drug development, critical knowledge gaps remain. Treating HCV infection during pregnancy and preventing HCV infection in children are two such gaps. More clinical trials focusing on the safety and efficacy of DAAs during pregnancy, infancy and early childhood are needed. Pregnancy registries could also provide important information as treatment is rolled out similar to the evidence gained by antiretroviral pregnancy registries. Through the use of antiretrovirals, prevention of mother-to-child transmission of HIV has been achieved and eliminating perinatal HIV transmission is now an attainable goal in the near future. This feat serves as a model for other disease areas and the use of newer antiviral agents is now proposed for prevention of breakthrough mother-to-child transmission of hepatitis B virus [80]. Lessons learned from preventing mother-to-child transmission of these two other viruses could benefit the field of HCV.

Treating HCV infection before and during pregnancy may lead to the prevention of vertical transmission and long-term infection in the infant. In addition to the health and psychological benefits for the mother and family, the economic burden of disease would also be alleviated. Demonstrating safety of DAAs during pregnancy as well as efficacy in preventing mother-to-child transmission of HCV could also lend further support to the argument for HCV screening for pregnant women.

7. Five-year view

Based on the current landscape of treatment of HCV with DAAs, in 5 years, we expect that more results from ongoing and planned clinical trials will be available and will help shape the discourse on HCV treatment policies of pregnant women and children. For children under 12 years old, we expect that DAA treatment options will be available. Economic analyses to support treatment of young children with DAAs will aid in treatment guidelines and policies. Considering the health and economic gains, children should have access to treatment, when indicated, regardless of cost. Policy changes for expanded screening during pregnancy (e.g. universal screening or expanded risk-based screening) may be implemented. Removing additional barriers to DAA access, such as cost [81], is also expected based on the current landscape.

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Declaration of interest

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Key issues

- HCV is a treatable disease, yet it accounts for more than a quarter of liver cirrhosis and hepatocellular carcinoma worldwide.
- There is evidence that HCV is increasing in the U.S. This increase has been associated with the ongoing opioid epidemic.
- Children that do not undergo spontaneous clearance of the virus will go on to develop chronic HCV infection.
- There are no treatment options currently for HCV-infected pregnant women and 6%–11% of them will pass on the virus to their infants.
- Screening of pregnant women is largely risk-based in the United States and women are required to self-identify as high-risk for HCV screening. Therefore, the opportunity to identify at-risk children may be missed if women do not self-report their risk correctly.
- Second and third generation DAAs have shown excellent results in treating HCV infection in adult and adolescent populations and have been approved for use in children 12 years of age and older.
- For younger children (<12 years old), there are no FDA approved DAAs yet. Preliminary results from clinical trials demonstrate the efficacy of DAAs in children 6–12 years old.
- DAAs may be the key to elimination of HCV. Although significant barriers such as cost and accessibility remain.
- More research and clinical trials are needed to provide the evidence that will help shape the horizon on pediatric infections and infections during pregnancy.