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**Vertically acquired hepatitis C virus infection: Correlates of transmission and disease progression**

Tovo PA *et al.* Vertical HCV infection

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**Abstract**

The worldwide prevalence of hepatitis C virus (HCV) infection in children is 0.05%- 0.4% in developed countries and 2%-5% in resource-limited settings, where inadequately tested blood products or un-sterile medical injections still remain important routes of infection. After the screening of blood donors, mother-to-child transmission (MTCT) of HCV has become the leading cause of pediatric infection, at a rate of 5%. Maternal HIV co-infection is a significant risk factor for MTCT and anti-HIV therapy during pregnancy seemingly can reduce the transmission rate of both viruses. Conversely, a high maternal viral load is an important, but not preventable risk factor, because at present no anti-HCV treatment can be administered to pregnant women to block viral replication. Caution is needed in adopting obstetric procedures, such as amniocentesis or internal fetal monitoring, that can favor fetal exposure to HCV contaminated maternal blood, though evidence is lacking on the real risk of single obstetric practices. Mode of delivery and type of feeding do not represent significant risk factors for MTCT. Therefore, there is no reason to offer elective Caesarean section or discourage breast-feeding to HCV infected parturients. Information on the natural history of vertical HCV infection is limited. The primary infection is asymptomatic in infants. At least one quarter of infected children shows a spontaneous viral clearance (SVC) that usually occurs within 6 years of life. IL-28B polymorphims and genotype 3 infection have been associated with greater chances of SVC. In general, HCV progression is mild or moderate in children with chronic infection who grow regularly, though cases with marked liver fibrosis or hepatic failure have been described. Non-organ specific autoantibodies and cryoglobulins are frequently found in children with chronic infection, but autoimmune diseases or HCV associated extrahepatic manifestations are rare.

**Key words**: Hepatitis C virus; Vertical transmission; Risk factors; Spontaneous viral clearance; Disease progression; Pediatrics

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**Core tip:** Approximately5% of exposed infants acquire hepatitis C virus (HCV) infection from the mother. Several correlates of vertical transmission have been identified, but no preventive intervention is available. Spontaneous viral clearance takes place in 25% of infected children within 6 years of age. Chronic infection has a mild/moderate course in the majority of children, though severe liver damage may develop. The new direct acting antiviral agents open exciting therapeutic perspectives for HCV infected children and offer an immediate opportunity to prevent the vertical transmission by reducing the burden of infected women of child-bearing age.

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**INTRODUCTION**

Hepatitis C virus (HCV) is a small, enveloped, single-strand RNA virus of the *Flaviviridae* family, which is transmitted *via* parenteral route[1]. In a high proportion of infected subjects the virus can persist and give rise to chronic liver disease, cirrhosis and hepatocellular carcinoma.

The total global prevalence of HCV infection is estimated to be 2%-3%, affecting approximately 160 million chronically infected individuals worldwide, with highly variable local prevalence rates between countries and within countries[2]. A recent literature review[3] described lower total global numbers (115 million HCV seropositive subjects, 80 million viremic infections), with a prevalence (1.6%) that might be decreasing. However, in other analyses the total disease burden is expected to increase in the next decade[4,5]. In fact, several risk factors have changed after the discovery of the virus. First of all, with the screening of blood donors the risk of contracting HCV from infected transfusions or blood products became extremely rare in resource-rich countries, where, conversely, needle exchange among intravenous drug users remains a paramount mode of horizontal transmission. Un-sterile medical injections and surgical procedures still remain a threat in a few regions of Africa[6]. Deaths due to long-lasting infections and immigration from high endemic areas may also play a role on the epidemiology of HCV infection, whereas the impact of antiviral treatments is irrelevant.

Few analyses have outlined the age distribution of HCV infection: a global number of 11 million anti-HCV positive children (< 15 years) has been calculated, with 5 million viremic infections[3]: such a surprising high proportion of infected children with spontaneous viral clearance (SVC) is presumably due to the intrinsic limits of these studies that can only partially reflect the real burden of infection.

Before the universal screening of blood products, pediatric HCV infection was predominantly due to iatrogenic transmission; then, mother-to-child transmission (MTCT) became the leading source of infection in childhood in developed countries. Notably, the increased safety of blood products and injection equipment also reduced the number of HCV infected women of childbearing age and consequently the number of vertical infections and the relative distribution of single genotypes. For instance, in Italy the total number of pediatric infections has been decreasing as well as the percentage of the transfusion-associated type 1b genotype, while the relative percentages of genotype 3 or 4 infections have been increasing[7]. On the other hand, many cases of hepatitis C in children and adolescents from resource-limited settings are still due to inadequately screened blood products and/or parenteral transmission[8,9]. These variations in risk factors account for the different prevalence of pediatric HCV infection that ranges from 0.05% to 0.36% in developed countries and from 1.8% to 5% in the developing world[10-12].

This review gives insights into the most relevant data about the risk of vertical HCV infection and correlates of transmission and highlights the evolution of the infection in children and adolescents.

**HCV INFECTION DURING PREGNANCY**

The prevalence of HCV infection in pregnant women mirrors that of the general population: ranging from 0.5%-2% in high-income countries to 5%-15% in some developing countries[13-16]. Most infected women do not develop HCV-mediated clinical manifestations during pregnancy, although an increase in gestational cholestasis has been described in some studies[17-19]. Indeed, there is a decrease of serum alanine aminotransferase (ALT) levels, a marker of liver cytolysis, in the advanced phase of pregnancy with concomitant increase in HCV viral load[16,20-22]. Conversely, in the post-partum period there is a rebound in ALT levels and a reduction in viral load[23-25]. Gestation is characterized by a down regulation of the immune responses[26], in particular of the T cell-mediated reactivity[27] with expansion of regulatory T cells[28], presumably to prevent maternal immune aggression against the fetus. This impaired cellular response on one hand may result in a reduced immune-mediated liver damage; on the other hand, it may favor the viral replication. In contrast, in the post-partum period the T-cell mediated cytotoxicity against HCV epitopes would recover with consequent decline in viral burden and rebound of liver injury.

A large observational study concluded that infants born to women with HCV infection appear to be at risk for poor birth outcomes, such as preterm delivery, low birth weight and congenital anomalies[29]. However, most studies did not evidence any increase in obstetric complications in HCV infected women[16,30,31]. Concomitant diseases, such as coagulation disorders or digestive tract malformations were also noticed in some vertically infected children, but these disorders do not appear HCV-related[32].

***Mother-to-child transmission of HCV***

The vertical HCV transmission rate is estimated to be about 5%, ranging from 3% to 10%[12,15,33-44]. These variations are mostly due to the small sample size of some investigations, differences in diagnostic criteria, population’s risk factors, type of study (retrospective or prospective), and duration of follow-up. The diagnosis of HCV infection in exposed infants is complicated by passively acquired maternal antibodies. These usually wane by 12 mo of age, but sometimes persist longer[45]. Furthermore, the first PCR assays were poorly standardized with consequent limits of sensitivity and specificity[46,47].

HCV can infect placental cells[48]. In addition, maternal cells can cross the placenta and reach the fetus. Therefore, fetal exposure to HCV would take place more frequently than actual in utero transmission. NK cells and NK T cells seem to play an important role in the clearance of acute HCV infection[49,50]. NK T cell and γδ T cell frequencies are higher in placenta from HCV-infected women and production of cytokines and cytotoxicity mediated by NK cells and NK T cells are increased in HCV-exposed placenta[51].

Vertical transmission takes place with every genotype. Studies on the quasispecies profile of HCV-infected infants revealed a limited diversity[52-55], suggesting that only a restricted number of viral variants, not dominant in the mother, are involved in mother-to-child transmission (MTCT). Characterization of circulating viral quasispecies during and after consecutive pregnancies in two women revealed loss of some escape mutations in HLA class I epitopes during pregnancy, presumably due to reduced cytotoxic T lymphocyte control. This was associated with emergence of viruses with optimized replicative fitness, which were also found in their infected children[56].

***When does HCV MTCT occur?***

We documented that one third of exposed infants ultimately shown to be infected are HCV RNA positive in the first 3 d of life, demonstrating that early in utero infection may occur; the others mostly become HCV RNA positive in the second/third month of life[57]. Interestingly, the time of appearance of viremia is similar in children vertically infected with HIV-1. This would suggest that the relative percentages of children infected before, during or post-delivery with either virus are comparable. However, in contrast to HIV-1, mode of delivery and type of feeding have no significant impact on HCV MTCT rate. Furthermore, the risk of transmitting HCV to the offspring is lower than HIV-1, despite the higher maternal viral load of the former, attesting that the underlying mechanisms and correlates of transmission are quite different for each virus.

**CORRELATES OF TRANSMISSION**

***Maternal viral load***

Vertical transmission is virtually restricted to women with detectable viremia[33,36,39,44,58-62], even though anecdotal cases from mothers with undetectable viremia have been reported[36,38,63-65]. A clear association between maternal viral load and risk of vertical transmission has been demonstrated: the higher the viral burden, the greater the risk of infection for the offspring. However, there is a broad overlap in the HCV RNA levels between transmitting and non-transmitting mothers and no threshold value has been identified to precisely quantify the risk of transmission.

HCV RNA is found in about 70% of seropositive pregnant women, but the percentage of viremic infections among antibody-positive women changes greatly in distinct geographical areas[2,3]: this might explain, in part, the different estimates of HCV MTCT rates from studies that did not take into consideration the maternal viremia.

HCV can infect and replicate in PBMCs and a relationship was found between HCV RNA in PBMCs of pregnant women and vertical transmission[66]. In this view, the HLA concordance between mother and offspring might facilitate the persistence of maternal cells in the newborn blood and the infection of newborn target cells (see below).

***HCV/HIV-1 co-infection***

The rate of HCV MTCT is increased when the mother is co-infected with HIV-1[35,37,39,41,67,68]; a recent meta-analysis concluded that maternal HIV co-infection is the most important determinant of vertical transmission risk (adjusted odds ratio 2.56; 95%CI: 1.50-4.43)[43]. The HIV-1-induced immunosuppression could lead to a higher HCV viral load, although this was not consistently observed[21]. In this context, when HIV/HCV co-infected pregnant women were treated with highly active antiretroviral therapy (HAART) the significant increase in HCV transmission disappeared[38,39]. It is worth noting that HIV-1 and HCV are mostly acquired independently from women with double infection, even though simultaneous transmission may occur.

***Obstetric factors and rupture of membranes***

HCV RNA has been detected in amniotic fluid, although inconsistently[69]. Amniocentesis was considered a likely explanation for diamniotic twins discordant for HCV infection, as the needle punctured the sac of one fetus[70]. However, in other diamniotic twins, only one was infected but amniocentesis was not performed[71]. Procedures that allow contact between maternal and fetal blood, such as amniocentesis, are expected to increase the risk of HCV transmission, though the limited studies available do not support this hypothesis[39,68]. Internal fetal monitoring was linked to a higher transmission rate[39] and a significant increase was observed in women who underwent perineal or vaginal lacerations, whereas episiotomy was irrelevant[59]. The duration of rupture of membranes (ROM) was longer in mothers of infected infants vs. uninfected infants[61,72]. This association also emerged by comparing a duration of ROM > 6 h[39] between transmitting and non-transmitting mothers. Antithetical results were reported by Delotte *et al*[68], who concluded that HCV infection does not appear to be a legitimate indication for modifying common obstetric practices.

***Mode of delivery***

Theoretically, elective caesarean section (CS) might reduce the HCV MTCT risk by preventing contact of the newborn with maternal blood during labor and infected genital secretions during the passage through the birth canal. Some studies observed a lower risk of infection in children born by CS[72-74]. However, the majority of targeted investigations, including the largest observational studies[20,36-38], consistently concluded that mode of delivery does not influence the HCV vertical transmission rate and such findings have been confirmed by a targeted meta-analysis[75]. Indeed, it is worth considering that elective CS might have protective effects in women with high viral load, a situation that has not been sufficiently analyzed. In fact, most expert recommendations or guidelines conclude that there is no reason to offer elective CS to HCV infected pregnant women[19,62,76-79].

***Type of feeding***

The data concerning the viral content in breast milk are contradictory[39,64,72,80,81], presumably following the differences in maternal viral load, methods used or portion of milk studied.

A few studies reported higher HCV transmission rates in breast-fed infants[64,72]. However, most results attest that type of feeding has no significant impact on the risk of HCV transmission[36-39,62,81]. Therefore, there is a consensus that breast-feeding should not be discouraged in HCV infected mothers[62,76-79]. However, these should consider abstaining from breast-feeding if their nipples are cracked or bleeding according to the Centers for Disease Control and Prevention (CDC)[78].

***Genetic background***

Few studies addressed the role of genetic factors in HCV MTCT. Differences in HLA system between mother and infant did not affect HCV transmission in one study[82]. Another investigation on concordance degree in HLA-DRB1 locus revealed that a HLA mismatch between mother and child was a protective factor, suggesting that alloreactive immune responses are involved in preventing HCV vertical transmission; in addition, maternal HLA-DRB104 correlated with protection, while HLA-DRB110 in children was a risk factor[83]. Others found that HLA-Cw\*07, -G\*010401, -DRB1\*0701, -DRB1\*1401 and homozygosis for HLA-G 14bp deletion can be considered as risk factors for HCV vertical transmission; on the contrary, protection was conferred by the HLA-DQB1\*06, -G\*0105N, -Cw\*0602, DRB1\*1104 and -DRB1\*1302 alleles[84]. The role of IL-28B polymorphisms on MTCT rate is irrelevant[60].

Cytokine gene polymorphisms, which affect the expression levels of the produced protein, were also investigated for TNF-α, interferon (IFN)-γ, IL-10, TGF-B1. No significant differences emerged between infected and uninfected children or between transmitting and non-transmitting mothers by comparing intermediate and low cytokine producers with high cytokine producers[83].

***Other factors***

Maternal age, number of pregnancies, prematurity, cigarette smoking, and alcohol intake have no significant impact on HCV MTCT rate. Discordant results were reported for IV drug use[42,72,85,86].

Notably, broadly reactive maternal neutralizing antibodies do not contribute to prevent vertical transmission[87,88].

A higher HCV transmission rate in females than in males emerged from a few studies[38,89]. Curiously, the same gender effect emerged for HIV[90,91] and human T-cell leukemia/lymphoma virus type I[92]. One wonders whether differences between males and females in hormonal or genetic background can modulate their immune response and thus their susceptibility to a few viral infections.

**NATURAL HISTORY OF VERTICALLY ACQUIRED HCV INFECTION**

The evolution of vertically acquired HCV infection is ill-defined, because there are few large prospective studies on children identified at birth and with prolonged follow-up, while the majority also include patients who acquired parenteral infections or who were referred to tertiary centers. Consequently, these analyses may underestimate the number of children with spontaneous clearance of infection and overestimate that of symptomatic children or with biochemical signs of hepatitis.

***Primary infection***

At birth and in the first weeks of life HCV infected newborns are asymptomatic and without any evidence of liver damage[93,94]. Subsequently, some infants exhibit high ALT levels, while others maintain normal or almost normal levels[94-96]. In general, acute HCV infection does not cause disturbances in infants, whereas in adults it may have a severe or even fatal evolution; furthermore, on average, ALT levels are considerably lower in the former.

Even if the fetal immune system can mount effector responses, *e.g.,* against cytomegalovirus[97], no specific T cell responses against HCV were observed in umbilical cord blood samples of exposed children[98].

***Spontaneous resolution of viremia***

In our large, prospective European study 20% of vertically infected children had a SVC by the age of 5 years[99]; in the cohort of our patients prospectively followed from birth, 27% cleared circulating HCV RNA over a 10-year period[32], and Yeung *et al*[100] observed that viremia disappeared in 25% of infected children, in comparable proportion between vertical and transfusional infections. More pessimistic estimates emerged from other studies, *e.g.,* loss of HCV RNA in 9%-11% of infected subjects[101,102]: these figures may be accounted for by the fact that also children not identified at birth were enrolled in the analyses. SVC is associated with biochemical remission of hepatitis and it usually occurs by 7 years of age[32,100,103]. Antiviral therapy should thus be postponed beyond the preschool age, unless in selected cases, in order to avoid useless treatments. Interestingly, children who reached SVC had higher ALT levels in the first two years of life when compared to those with persistent infection[32,95], as if a stronger cytolytic effect would mirror a more vigorous immune response ultimately resulting in resolution of infection.

Understanding the mechanisms responsible for SVC plays a crucial role for development of future vaccines. Both viral and host factors have been associated with SVC, such as genotype 3 infection[32,95] or positive IFN-γ responses against structural and non-structural recombinant HCV antigens[104]. Furthermore, children with the rs 12979860 single-nucleotide C/C polymorphism located on chromosome 19q13.13, upstream of the interleukin 28B gene, have a higher probability of SVC[105,106], particularly with genotype 1 infection[60]. IL-28B is one of the three IFN-γ genes that code type III IFNs. These elicit the transcription of interferon-stimulated genes that are responsible for antiviral activity. Therefore, variations in genes involved in the immune response against the virus influence the spontaneous clearance of HCV. The aforementioned marked differences in the percentage of viremic subjects in distinct areas of the world further support the importance of the genetic background in favoring the resolution of viremia, though even the different distribution of viral genotypes could have a role[3].

***Humoral immunity***

A few HCV RNA-positive, antibody-negative asymptomatic children have been described[60,65,94]. However, virtually all vertically infected children develop specific antibodies against HCV. These persist even after SVC, although a fraction of these subjects can serorevert after many years[32].

The presence of cross-reactive neutralizing antibodies during the chronic phase of infection does not correlate with better control of viremia[88]. In contrast, the humoral response drives the evolution of viral quasispecies (see below).

***Chronic HCV infection***

The chronic infection has a different clinical course in children as compared to adults. Every study highlights that HCV progression is minimal or mild in children, though severe hepatic damage may develop and liver transplantation may be required[12,13,44,95,96,99,101,102,107]. Hepatocellular carcinoma is extremely rare and, to our knowledge, it was described only in one adolescent with possible vertical infection[108]. Children grow regularly without variations from normal height and weight ranges[109], only a quarter develop hepatomegaly in the first decade of life[99], and they disclose mild variations in peripheral lymphocytes and neutrophils[110].

A broad range of ALT concentrations has been observed in vertically infected children: the majority shows modest alterations. ALT levels are highest in the first two years of life then decline[94]; from the practical point of view, they are not a reliable prognostic marker, because they are poorly predictive of the underlying liver damage.

A wide spectrum of histopathological alterations has been found in the liver of children with vertical infection. The characteristic lesions of chronic hepatitis C described in adults, such a steatosis, sinusoidal and portal aggregates of lymphocytes, and bile duct abnormalities have been observed also in children. Based on signs of structural alterations, inflammatory activity, and necrosis, the grade of disease usually varies from minimal to moderate; however, a few children show variable degrees of fibrosis or, rarely, pictures of overt cirrhosis[94-96,107,111-113]. Liver biopsy is not a routine procedure in the management of HCV infected children; transient elastography may help, distinguishing the evolution of liver fibrosis over time[32].

***Viral quasispecies***

One of the most important characteristics of HCV is its capacity to mutate very quickly. In addition, it can impair both the innate and adaptive host’s immune response, *e.g.,* by inhibiting the activation of dendritic cells, the IFN production, and by evading or exhausting the T cell responses[114] . The consequence is a persistent infection with many viral variants (quasispecies) replicating simultaneously in each infected individual.

The impact of the evolution of viral quasispecies on the course of pediatric HCV infection has been examined in several studies with contrasting results. We observed that children who developed hepatic damage had mono- or oligoclonal populations of viral variants, whereas heterogeneous viral quasispecies emerged in those with mild or no liver damage, in coincidence with the appearance of anti-HCV antibodies[55]. High ALT levels might be the result of a vigorous cell-mediated immune response against the virus, while normal ALT levels would result from an absent or weak cellular response in the presence of a robust humoral response; the latter could exert strong selective pressures leading to a broad spectrum of HCV quasispecies. A mechanism of long-lasting nucleotide invariability with purifying selection operating on the HVR1 has been confirmed[115]. However, others[54] found that changes in the HVR-1 sequence occurred irrespective of the ALT profile; indeed, the study population included only children > 1 year, whereas the diversification of the HCV population takes place between 6 and 12 mo after birth[52].

The importance of humoral response in determining the evolution of quasispecies is further supported by limited or no variations in a persistently seronegative child[65], in children and adults suffering from agammaglobulinemia[116], and in children with HIV-1 co-infection whose humoral response is defective[53,117].

***Extrahepatic manifestations***

A wide array of extrahepatic manifestations has been associated with chronic HCV infection. Among these, mixed cryoglobulinemia is the most frequent in adults[118]. It is due to an unregulated clonal expansion of B-lymphocytes, which may give rise to membrano-proliferative glomerulonephritis in one third of cases, to purpura, arthralgia, peripheral neuropathy and ultimately it may evolve in non-Hodgkin’s lymphoma. Mixed cryoglubulinemia had not been described in children. In our cohort of 45 children prospectively followed-up from birth, surprisingly we found that one third developed cryoglobulins at a median age of 6.6 years (range 2.0–13.3 years) and two affected adolescents initially exhibited C4 reduction and then developed mild persistent proteinuria[32]. In fact, membrano-proliferative glomerulonephritis may occur in children with chronic HCV infection[119,120].

Non-organ specific autoantibodies (NOSAs) are frequently detected in subjects with chronic hepatitis C, including children. Anti-liver-kidney microsomal type-1 (LKM-1) antibody seems peculiar of HCV infection: it was found in 2-%15% of children with chronic infection[32,121-123] and LKM-1-positive children had a more advanced liver disease than LKM-1-negative children[124]. In general, the pathogenetic role of NOSAs remains to be elucidated and autoantibodies do not predict liver fibrosis progression[125]. Despite the high prevalence of NOSAs, autoimmune diseases are rare in HCV infected children and adolescents[126].

In a series of 36 subjects, 4 had subclinical hypothyroidism without antithyroid antibody and 2 antithyiroglobulin antibody with normal TSH levels [127].

The presence of cryoglobulins and autoantibodies represents the chronic stimulation of the immune system by HCV by mechanisms such as molecular mimicry or interactions between the HCV E2 protein and CD81 molecule expressed by B-lymphocytes[128]. It must be underlined that sometimes cryoglobulins or NOSAs developed or persisted even after SVC[32], suggesting that HCV can elicit a chain of events within the immune system that can proceed independently from active viral replication. Whether this might give rise to significant morbidity even after SVC remains to be verified. On the other hand, HCV RNA has been detected in liver and/or in PBMCs of seropositive subjects after disappearance of serum/plasma viremia[128,129]. Furthermore, recent studies show that after successful interferon-based treatment, HCV traces are still detectable and this correlates with a peak of HCV-specific CTL response[130]. Therefore, this occult infection might be responsible for virus-induced immune reactions in sustained responders. HCV does not integrate into the host genome. Whether HCV persists in the liver in a form that is also refractory to eradication by successful DAA treatment has to be evaluated in long-term follow-up studies.

Anecdotally, other associations of chronic HCV infection and extrahepatic disorders have been described, such as diabetes[32,131], inflammatory myopathy[130], and opsoclonus-myoclonus syndrome[132].

**CONCLUSION**

HCV infection affects a large number of women of child-bearing age worldwide, and transmission of the virus from mother to child remains a serious public health problem.

Several correlates of vertical transmission have been identified; however, none is modifiable and no interventions can prevent or reduce the transmission risk, with the exception of anti-HIV treatment in women with HIV/HCV co-infection. In particular, there is no reason to offer elective Caesarean section or discourage lactation in infected mothers. The lack of effective preventive measures is not a contraindication for pregnancy; on the other hand, it makes useless the routine screening for the diagnosis of HCV infection in pregnant women. Invasive obstetric procedures favoring the contact with contaminated maternal blood should be avoided, though specific evidence is lacking.

The reduced reactivity of the immune system during pregnancy is presumably responsible for the increased viral replication in the third trimester of gestation, a condition that might facilitate the virus transmission to the offspring. Despite the massive exposure of the fetus to viral particles and maternal HCV-infected PBMCs, the rate of MTCT is surprisingly low when compared to other viral infections, such as HIV-1, a further proof that different defensive mechanisms protect the offspring from distinct maternal viral infections. Further research is needed to better define these mechanisms and understand the innate and adaptive immune responses that regulate the host-virus interactions, so that new therapeutic strategies and preventive vaccines can be developed.

There is a clear association between maternal viral load and risk of HCV vertical transmission. An antiviral treatment during pregnancy in HCV RNA-positive women is expected to reduce significantly the MTCT rate. Theoretically, the IFN-free and ribavirin-free therapeutic regimens might represent an exciting perspective, because the new direct acting antiviral agents (DAAs) can give rise to a dramatic reduction in plasma HCV RNA level in few weeks[133]. However, at present they cannot be used in pregnant women, because any risk of toxic effects on the fetus must be excluded. Meanwhile, a significant decrease in vertical infections may derive, indirectly, from using these highly effective, pan-genotypic DAAs in infected women of child-bearing age.

Spontaneous clearance of vertically acquired HCV infection occurs in at least one quarter of cases during childhood. Children with genotype 3 infection or polymorphisms of IL-28B gene locus or higher ALT levels in the first two years of life have greater chances of SVC. Since this mostly takes place in preschool age, postponing antiviral treatments beyond this age seems appropriate in the great majority of cases.

Chronic infection is generally asymptomatic in childhood, although a low to moderate level of hepatomegaly and liver fibrosis may develop. Most infected children grow regularly and have a good quality of life. Occasionally, HCV can however progress, leading to severe liver disease or hepatic failure. Although the importance of a few viral or host factors are emerging, in the daily practice there are no reliable early prognostic markers. With the new drugs on the horizon, the possibility to better outline the natural history of vertically acquired HCV infection is waning. Who and when should be treated remains thus questionable. The answer is presumably every HCV infected child, provided that the ongoing trials confirm the safety and effectiveness of the new DAAs in children and, last but not least, their costs are affordable for a generalized use.

The presence of NOSAs and cryoglobulins is frequent in HCV infected children and adolescents, whereas associated clinical manifestations are rare. Larger prospective studies possibly following children through the adult age are needed to clarify the influence of the vertical infection on the immune system and on the development of autoimmune diseases. The next availability of DAAs is expected to represent a paramount cornerstone for blocking not only the HCV-driven liver damage, but also the associated extrahepatic disorders.

**REFERENCES**

1 **Choo QL**, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989; **244**: 359-362 [PMID: 2523562 DOI: 10.1126/science.2523562]

2 **Lavanchy D**. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect* 2011; **17**: 107-115 [PMID: 21091831 DOI: 10.1111/j.1469-0691.2010.03432.x]

3 **Gower E**, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* 2014; **61**: S45-S57 [PMID: 25086286 DOI: 10.1016/j.jhep.2014.07.027]

4 **Mohd Hanafiah K**, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; **57**: 1333-1342 [PMID: 23172780 DOI: 10.1002/hep.26141]

5 **Wedemeyer H**, Dore GJ, Ward JW. Estimates on HCV disease burden worldwide - filling the gaps. *J Viral Hepat* 2015; **22 Suppl 1**: 1-5 [PMID: 25560838 DOI: 10.1111/jvh.12371]

6 **Mohamoud YA**, Mumtaz GR, Riome S, Miller D, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. *BMC Infect Dis* 2013; **13**: 288 [PMID: 23799878 DOI: 10.1186/1471-2334-13-288]

7 **Gimelfarb A**. Pleiotropy and multilocus polymorphisms. *Genetics* 1992; **130**: 223-227 [PMID: 1732163 DOI: 10.1016/j.jhep.2006.12.014]

8 **Akhtar S**, Moatter T. Intra-household clustering of hepatitis C virus infection in Karachi, Pakistan. *Trans R Soc Trop Med Hyg* 2004; **98**: 535-539 [PMID: 15251402 DOI: 10.1016/j.trstmh.2003.12.010]

9 **Miller FD**, Abu-Raddad LJ. Evidence of intense ongoing endemic transmission of hepatitis C virus in Egypt. *Proc Natl Acad Sci U S A* 2010; **107**: 14757-14762 [PMID: 20696911 DOI: 10.1073/pnas.1008877107]

10 **Schwimmer JB**, Balistreri WF. Transmission, natural history, and treatment of hepatitis C virus infection in the pediatric population. *Semin Liver Dis* 2000; **20**: 37-46 [PMID: 10895430 DOI: 10.1055/s-2000-9257]

11 **Jafri W**, Jafri N, Yakoob J, Islam M, Tirmizi SF, Jafar T, Akhtar S, Hamid S, Shah HA, Nizami SQ. Hepatitis B and C: prevalence and risk factors associated with seropositivity among children in Karachi, Pakistan. *BMC Infect Dis* 2006; **6**: 101 [PMID: 16792819 DOI: 10.1186/1471-2334-6-101]

12 **El-Shabrawi MH**, Kamal NM. Burden of pediatric hepatitis C. *World J Gastroenterol* 2013; **19**: 7880-7888 [PMID: 24307782 DOI: 10.3748/wjg.v19.i44.7880]

13 **Zahran KM**, Badary MS, Agban MN, Abdel Aziz NH. Pattern of hepatitis virus infection among pregnant women and their newborns at the Women's Health Center of Assiut University, Upper Egypt. *Int J Gynaecol Obstet* 2010; **111**: 171-174 [PMID: 20708181 DOI: 10.1016/j.ijgo.2010.06.013]

14 **Arshad M**, El-Kamary SS, Jhaveri R. Hepatitis C virus infection during pregnancy and the newborn period--are they opportunities for treatment? *J Viral Hepat* 2011; **18**: 229-236 [PMID: 21392169 DOI: 10.1111/j.1365-2893.2010.01413.x]

15 **Le Campion A**, Larouche A, Fauteux-Daniel S, Soudeyns H. Pathogenesis of hepatitis C during pregnancy and childhood. *Viruses* 2012; **4**: 3531-3550 [PMID: 23223189 DOI: 10.3390/v4123531]

16 **Floreani A**. Hepatitis C and pregnancy. *World J Gastroenterol* 2013; **19**: 6714-6720 [PMID: 24187446 DOI: 10.3748/wjg.v19.i40.6714]

17 **Locatelli A**, Roncaglia N, Arreghini A, Bellini P, Vergani P, Ghidini A. Hepatitis C virus infection is associated with a higher incidence of cholestasis of pregnancy. *Br J Obstet Gynaecol* 1999; **106**: 498-500 [PMID: 10430202 DOI: 10.1111/j.1471-0528.1999.tb08305.x]

18 **Paternoster DM**, Fabris F, Palù G, Santarossa C, Bracciante R, Snijders D, Floreani A. Intra-hepatic cholestasis of pregnancy in hepatitis C virus infection. *Acta Obstet Gynecol Scand* 2002; **81**: 99-103 [PMID: 11942897 DOI: 10.1034/j.1600-0412.2002.810202.x]

19 **Dunkelberg JC**, Berkley EM, Thiel KW, Leslie KK. Hepatitis B and C in pregnancy: a review and recommendations for care. *J Perinatol* 2014; **34**: 882-891 [PMID: 25233195 DOI: 10.1038/jp.2014.167]

20 **Conte D**, Fraquelli M, Prati D, Colucci A, Minola E. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology* 2000; **31**: 751-755 [PMID: 10706568 DOI: 10.1002/hep.510310328]

21 **Gervais A**, Bacq Y, Bernuau J, Martinot M, Auperin A, Boyer N, Kilani A, Erlinger S, Valla D, Marcellin P. Decrease in serum ALT and increase in serum HCV RNA during pregnancy in women with chronic hepatitis C. *J Hepatol* 2000; **32**: 293-299 [PMID: 10707870 DOI: 10.1016/S0168-8278(00)80075-6]

22 **Paternoster DM**, Santarossa C, Grella P, Palù G, Baldo V, Boccagni P, Floreani A. Viral load in HCV RNA-positive pregnant women. *Am J Gastroenterol* 2001; **96**: 2751-2754 [PMID: 11569706 DOI: 10.1111/j.1572-0241.2001.04135.x]

23 **Vento S**, Longhi MS, Cainelli F, Concia E. Effect of pregnancy on chronic hepatitis C. *Lancet* 2001; **357**: 389-390 [PMID: 11211018 DOI: 10.1016/S0140-6736(05)71517-8]

24 **Geissler W**. [Active rehabilitation of myocardial infarct]. *Z Arztl Fortbild (Jena)* 1975; **29**: 306-308 [PMID: 1220308 DOI: 10.1007/s005350200105]

25 **Latt NC**, Spencer JD, Beeby PJ, McCaughan GW, Saunders JB, Collins E, Cossart YE. Hepatitis C in injecting drug-using women during and after pregnancy. *J Gastroenterol Hepatol* 2000; **15**: 175-181 [PMID: 10735542 DOI: 10.1046/j.1440-1746.2000.02060.x]

26 **Munoz-Suano A**, Hamilton AB, Betz AG. Gimme shelter: the immune system during pregnancy. *Immunol Rev* 2011; **241**: 20-38 [PMID: 21488887 DOI: 10.1111/j.1600-065X.2011.01002.x]

27 **Watanabe M**, Iwatani Y, Kaneda T, Hidaka Y, Mitsuda N, Morimoto Y, Amino N. Changes in T, B, and NK lymphocyte subsets during and after normal pregnancy. *Am J Reprod Immunol* 1997; **37**: 368-377 [PMID: 9196795 DOI: 10.1111/j.1600-0897.1997.tb00246.x]

28 **Somerset DA**, Zheng Y, Kilby MD, Sansom DM, Drayson MT. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. *Immunology* 2004; **112**: 38-43 [PMID: 15096182 DOI: 10.1111/j.1365-2567.2004.01869.x]

29 **Safir A**, Levy A, Sikuler E, Sheiner E. Maternal hepatitis B virus or hepatitis C virus carrier status as an independent risk factor for adverse perinatal outcome. *Liver Int* 2010; **30**: 765-770 [PMID: 20214739 DOI: 10.1111/j.1478-3231.2010.02218.x]

30 **Jabeen T**, Cannon B, Hogan J, Crowley M, Devereux C, Fanning L, Kenny-Walsh E, Shanahan F, Whelton MJ. Pregnancy and pregnancy outcome in hepatitis C type 1b. *QJM* 2000; **93**: 597-601 [PMID: 10984554 DOI: 10.1093/qjmed/93.9.597]

31 **Floreani A**, Paternoster D, Zappala F, Cusinato R, Bombi G, Grella P, Chiaramonte M. Hepatitis C virus infection in pregnancy. *Br J Obstet Gynaecol* 1996; **103**: 325-329 [PMID: 8605128 DOI: 10.1111/j.1471-0528.1996.tb09736.x]

32 **Garazzino S**, Calitri C, Versace A, Alfarano A, Scolfaro C, Bertaina C, Vatrano S, Mignone F, Licciardi F, Gabiano C, Tovo PA. Natural history of vertically acquired HCV infection and associated autoimmune phenomena. *Eur J Pediatr* 2014; **173**: 1025-1031 [PMID: 24585099 DOI: 10.1007/s00431-014-2286-6]

33 **Ohto H**, Terazawa S, Sasaki N, Sasaki N, Hino K, Ishiwata C, Kako M, Ujiie N, Endo C, Matsui A. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. *N Engl J Med* 1994; **330**: 744-750 [PMID: 8107740 DOI: 10.1056/NEJM199403173301103]

34 **Zanetti AR**, Tanzi E, Paccagnini S, Principi N, Pizzocolo G, Caccamo ML, D'Amico E, Cambiè G, Vecchi L. Mother-to-infant transmission of hepatitis C virus. Lombardy Study Group on Vertical HCV Transmission. *Lancet* 1995; **345**: 289-291 [PMID: 7530793 DOI: 10.1016/S0140-6736(95)90277-5]

35 **Tovo PA**, Palomba E, Ferraris G, Principi N, Ruga E, Dallacasa P, Maccabruni A. Increased risk of maternal-infant hepatitis C virus transmission for women coinfected with human immunodeficiency virus type 1. Italian Study Group for HCV Infection in Children. *Clin Infect Dis* 1997; **25**: 1121-1124 [PMID: 9402369 DOI: 10.1086/516102]

36 **Resti M**, Azzari C, Mannelli F, Moriondo M, Novembre E, de Martino M, Vierucci A. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. *BMJ* 1998; **317**: 437-441 [PMID: 9703524 DOI: 10.1136/bmj.317.7156.43]

37 **European Paediatric Hepatitis C Virus Network**. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. European Paediatric Hepatitis C Virus Network. *BJOG* 2001; **108**: 371-377 [PMID: 11305543 DOI: 10.1111/j.1471-0528.2001.00088.x]

38 **European Paediatric Hepatitis C Virus Network**. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis* 2005; **192**: 1872-1879 [PMID: 16267757 DOI: 10.1086/497695]

39 **Mast EE**, Hwang LY, Seto DS, Nolte FS, Nainan OV, Wurtzel H, Alter MJ. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis* 2005; **192**: 1880-1889 [PMID: 16267758 DOI: 10.1086/497701]

40 **Tovo PA**, Lazier L, Versace A. Hepatitis B virus and hepatitis C virus infections in children. *Curr Opin Infect Dis* 2005; **18**: 261-266 [PMID: 15864105]

41 **Mariné-Barjoan E**, Berrébi A, Giordanengo V, Favre SF, Haas H, Moreigne M, Izopet J, Tricoire J, Tran A, Pradier C, Bongain A. HCV/HIV co-infection, HCV viral load and mode of delivery: risk factors for mother-to-child transmission of hepatitis C virus? *AIDS* 2007; **21**: 1811-1815 [PMID: 17690581 DOI: 10.1097/QAD.0b013e3282703810]

42 **Azzari C**, Moriondo M, Indolfi G, Betti L, Gambineri E, de Martino M, Resti M. Higher risk of hepatitis C virus perinatal transmission from drug user mothers is mediated by peripheral blood mononuclear cell infection. *J Med Virol* 2008; **80**: 65-71 [PMID: 18041020 DOI: 10.1002/jmv.21023]

43 **Benova L**, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis* 2014; **59**: 765-773 [PMID: 24928290 DOI: 10.1093/cid/ciu447]

44 **Yeung CY**, Lee HC, Chan WT, Jiang CB, Chang SW, Chuang CK. Vertical transmission of hepatitis C virus: Current knowledge and perspectives. *World J Hepatol* 2014; **6**: 643-651 [PMID: 25276280 DOI: 10.4254/wjh.v6.i9.643]

45 **England K**, Pembrey L, Tovo PA, Newell ML. Excluding hepatitis C virus (HCV) infection by serology in young infants of HCV-infected mothers. *Acta Paediatr* 2005; **94**: 444-450 [PMID: 16092459 DOI: 10.1111/j.1651-2227.2005.tb01916.x]

46 **Pembrey L**, Newell ML, Tovo PA, van Drimmelen H, Quinti I, Furlini G, Galli S, Meliconi MG, Burns S, Hallam N, Sönnerborg A, Cilla G, Serrano E, Laccetti P, Portella G, Polywka S, Icardi G, Bruzzone B, Balbo L, Alfarano A. Inter-laboratory comparison of HCV-RNA assay results: implications for multi-centre research. *J Med Virol* 2003; **69**: 195-201 [PMID: 12683407 DOI: 10.1002/jmv.10283]

47 **Polywka S**, Pembrey L, Tovo PA, Newell ML. Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection. *J Med Virol* 2006; **78**: 305-310 [PMID: 16372293 DOI: 10.1002/jmv.20540]

48 **Nie QH**, Gao LH, Cheng YQ, Huang XF, Zhang YF, Luo XD, Wang JQ, Wang YY. Hepatitis C virus infection of human cytotrophoblasts cultured in vitro. *J Med Virol* 2012; **84**: 1586-1592 [PMID: 22930506 DOI: 10.1002/jmv.23380]

49 **Pelletier S**, Drouin C, Bédard N, Khakoo SI, Bruneau J, Shoukry NH. Increased degranulation of natural killer cells during acute HCV correlates with the magnitude of virus-specific T cell responses. *J Hepatol* 2010; **53**: 805-816 [PMID: 20688412 DOI: 10.1016/j.jhep.2010.05.013]

50 **Alter G**, Jost S, Rihn S, Reyor LL, Nolan BE, Ghebremichael M, Bosch R, Altfeld M, Lauer GM. Reduced frequencies of NKp30+NKp46+, CD161+, and NKG2D+ NK cells in acute HCV infection may predict viral clearance. *J Hepatol* 2011; **55**: 278-288 [PMID: 21168454 DOI: 10.1016/j.jhep.2010.11.030]

51 **Hurtado CW**, Golden-Mason L, Brocato M, Krull M, Narkewicz MR, Rosen HR. Innate immune function in placenta and cord blood of hepatitis C--seropositive mother-infant dyads. *PLoS One* 2010; **5**: e12232 [PMID: 20814429 DOI: 10.1371/journal.pone.0012232.2]

52 **Manzin A**, Solforosi L, Debiaggi M, Zara F, Tanzi E, Romanò L, Zanetti AR, Clementi M. Dominant role of host selective pressure in driving hepatitis C virus evolution in perinatal infection. *J Virol* 2000; **74**: 4327-4334 [PMID: 10756048 DOI: 10.1128/JVI.74.9.4327-4334.2000]

53 **Pollack H**, Hou Z, Hughes AL, Borkowsky W. Perinatal transmission and viral evolution of hepatitis C virus quasispecies in infants coinfected with HIV. *J Acquir Immune Defic Syndr* 2004; **36**: 890-899 [PMID: 15220695 DOI: 10.1097/00126334-200408010-00002]

54 **Gerotto M**, Resti M, Dal Pero F, Migliorato I, Alberti A, Bortolotti F. Evolution of hepatitis C virus quasispecies in children with chronic hepatitis C. *Infection* 2006; **34**: 62-65 [PMID: 16703294 DOI: 10.1007/s15010-006-5037-4]

55 **Austgen TR**, Chen MK, Moore W, Souba WW. Endotoxin and renal glutamine metabolism. *Arch Surg* 1991; **126**: 23-27 [PMID: 1670757 DOI: 10.1073/pnas.0602546103]

56 **Honegger JR**, Kim S, Price AA, Kohout JA, McKnight KL, Prasad MR, Lemon SM, Grakoui A, Walker CM. Loss of immune escape mutations during persistent HCV infection in pregnancy enhances replication of vertically transmitted viruses. *Nat Med* 2013; **19**: 1529-1533 [PMID: 24162814 DOI: 10.1038/nm.3351]

57 **Mok J**, Pembrey L, Tovo PA, Newell ML. When does mother to child transmission of hepatitis C virus occur? *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F156-F160 [PMID: 15724041 DOI: 10.1136/adc.2004.059436]

58 **Lin HH**, Kao JH, Hsu HY, Ni YH, Yeh SH, Hwang LH, Chang MH, Hwang SC, Chen PJ, Chen DS. Possible role of high-titer maternal viremia in perinatal transmission of hepatitis C virus. *J Infect Dis* 1994; **169**: 638-641 [PMID: 8158040 DOI: 10.1093/infdis/169.3.638]

59 **Steininger C**, Kundi M, Jatzko G, Kiss H, Lischka A, Holzmann H. Increased risk of mother-to-infant transmission of hepatitis C virus by intrapartum infantile exposure to maternal blood. *J Infect Dis* 2003; **187**: 345-351 [PMID: 12552417 DOI: 10.1086/367704]

60 **Tomura Y**, Hisa H, Satoh S. Effects of atrial natriuretic peptide on phenylephrine-induced renin release in dogs. *Clin Exp Pharmacol Physiol* 1990; **17**: 381-384 [PMID: 2141305 DOI: 10.1002/hep.24298.2011]

61 **Murakami J**, Nagata I, Iitsuka T, Okamoto M, Kaji S, Hoshika T, Matsuda R, Kanzaki S, Shiraki K, Suyama A, Hino S. Risk factors for mother-to-child transmission of hepatitis C virus: Maternal high viral load and fetal exposure in the birth canal. *Hepatol Res* 2012; **42**: 648-657 [PMID: 22404371 DOI: 10.1111/j.1872-034X.2012.00968.x]

62 **Cottrell EB**, Chou R, Wasson N, Rahman B, Guise JM. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013; **158**: 109-113 [PMID: 23437438 DOI: 10.7326/0003-4819-158-2-201301150-00574]

63 **Dore GJ**, Kaldor JM, McCaughan GW. Systematic review of role of polymerase chain reaction in defining infectiousness among people infected with hepatitis C virus. *BMJ* 1997; **315**: 333-337 [PMID: 9270453 DOI: 10.1136/bmj.315.7104.333]

64 **Ruiz-Extremera A**, Salmerón J, Torres C, De Rueda PM, Giménez F, Robles C, Miranda MT. Follow-up of transmission of hepatitis C to babies of human immunodeficiency virus-negative women: the role of breast-feeding in transmission. *Pediatr Infect Dis J* 2000; **19**: 511-516 [PMID: 10877164]

65 **Larouche A**, Gaëtan G, El-Bilali N, Quesnel-Vallières M, Martin SR, Alvarez F, Shoukry NH, Soudeyns H. Seronegative hepatitis C virus infection in a child infected via mother-to-child transmission. *J Clin Microbiol* 2012; **50**: 2515-2519 [PMID: 22535990 DOI: 10.1128/JCM.00622-12]

66 **Azzari C**, Resti M, Moriondo M, Ferrari R, Lionetti P, Vierucci A. Vertical transmission of HCV is related to maternal peripheral blood mononuclear cell infection. *Blood* 2000; **96**: 2045-2048 [PMID: 10979945]

67 **Papaevangelou V**, Pollack H, Rochford G, Kokka R, Hou Z, Chernoff D, Hanna B, Krasinski K, Borkowsky W. Increased transmission of vertical hepatitis C virus (HCV) infection to human immunodeficiency virus (HIV)-infected infants of HIV- and HCV-coinfected women. *J Infect Dis* 1998; **178**: 1047-1052 [PMID: 9806033 DOI: 10.1086/515668]

68 **Delotte J**, Barjoan EM, Berrébi A, Laffont C, Benos P, Pradier C, Bongain A. Obstetric management does not influence vertical transmission of HCV infection: results of the ALHICE group study. *J Matern Fetal Neonatal Med* 2014; **27**: 664-670 [PMID: 23971940 DOI: 10.3109/14767058.2013.829813]

69 **Delamare C**, Carbonne B, Heim N, Berkane N, Petit JC, Uzan S, Grangé JD. Detection of hepatitis C virus RNA (HCV RNA) in amniotic fluid: a prospective study. *J Hepatol* 1999; **31**: 416-420 [PMID: 10488698 DOI: 10.1016/S0168-8278(99)80031-2]

70 **Minola E**, Maccabruni A, Pacati I, Martinetti M. Amniocentesis as a possible risk factor for mother-to-infant transmission of hepatitis C virus. *Hepatology* 2001; **33**: 1341-1342 [PMID: 11343269 DOI: 10.1053/jhep.2001.0103305le02]

71 **Inui A**, Fujisawa T, Sogo T, Komatsu H, Isozaki A, Sekine I. Different outcomes of vertical transmission of hepatitis C virus in a twin pregnancy. *J Gastroenterol Hepatol* 2002; **17**: 617-619 [PMID: 12084037 DOI: 10.1046/j.1440-1746.2002.02601.x]

72 **Spencer JD**, Latt N, Beeby PJ, Collins E, Saunders JB, McCaughan GW, Cossart YE. Transmission of hepatitis C virus to infants of human immunodeficiency virus-negative intravenous drug-using mothers: rate of infection and assessment of risk factors for transmission. *J Viral Hepat* 1997; **4**: 395-409 [PMID: 9430360 DOI: 10.1046/j.1365-2893.1997.00073.x]

73 **Okamoto M**, Nagata I, Murakami J, Kaji S, Iitsuka T, Hoshika T, Matsuda R, Tazawa Y, Shiraki K, Hino S. Prospective reevaluation of risk factors in mother-to-child transmission of hepatitis C virus: high virus load, vaginal delivery, and negative anti-NS4 antibody. *J Infect Dis* 2000; **182**: 1511-1514 [PMID: 11023474 DOI: 10.1086/315883]

74 **Gibb DM**, Goodall RL, Dunn DT, Healy M, Neave P, Cafferkey M, Butler K. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000; **356**: 904-907 [PMID: 11036896 DOI: 10.1016/S0140-6736(00)02681-7]

75 **Ghamar Chehreh ME**, Tabatabaei SV, Khazanehdari S, Alavian SM. Effect of cesarean section on the risk of perinatal transmission of hepatitis C virus from HCV-RNA+/HIV- mothers: a meta-analysis. *Arch Gynecol Obstet* 2011; **283**: 255-260 [PMID: 20652289 DOI: 10.1007/s00404-010-1588-9]

76 **Pembrey L**, Newell ML, Tovo PA. The management of HCV infected pregnant women and their children European paediatric HCV network. *J Hepatol* 2005; **43**: 515-525 [PMID: 16144064 DOI: 10.1016/j.jhep.2005.06.002]

77 **Shiraki K**, Ohto H, Inaba N, Fujisawa T, Tajiri H, Kanzaki S, Matsui A, Morishima T, Goto K, Kimura A, Hino S. Guidelines for care of pregnant women carrying hepatitis C virus and their infants. *Pediatr Int* 2008; **50**: 138-140 [PMID: 18279227 DOI: 10.1111/j.1442-200X.2007.02518.x]

78 **Workowski KA**, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010; **59**: 1-110 [PMID: 21160459]

79 **Shaheen MA**, Idrees M. Evidence-based consensus on the diagnosis, prevention and management of hepatitis C virus disease. *World J Hepatol* 2015; **7**: 616-627 [PMID: 25848486 DOI: 10.4254/wjh.v7.i3.616]

80 **Kage M**, Ogasawara S, Kosai K, Nakashima E, Shimamatsu K, Kojiro M, Kimura A, Fujisawa T, Matsukuma Y, Ito Y, Kondo S, Kawano K, Sata M. Hepatitis C virus RNA present in saliva but absent in breast-milk of the hepatitis C carrier mother. *J Gastroenterol Hepatol* 1997; **12**: 518-521 [PMID: 9257243 DOI: 10.1111/j.1440-1746.1997.tb00476.x]

81 **Polywka S**, Schröter M, Feucht HH, Zöllner B, Laufs R. Low risk of vertical transmission of hepatitis C virus by breast milk. *Clin Infect Dis* 1999; **29**: 1327-1329 [PMID: 10524987 DOI: 10.1086/313473]

82 **Azzari C**, Indolfi G, Betti L, Moriondo M, Massai C, Becciolini L, Bertelli L, Poggi GM, De Martino M, Resti M. Vertical hepatitis C virus transmission is not related to mother-child class-1 HLA concordance. *Int J Immunopathol Pharmacol* 2000; **20**: 827-831 [PMID: 18179755]

83 **Bevilacqua E**, Fabris A, Floreano P, Pembrey L, Newell ML, Tovo PA, Amoroso A. Genetic factors in mother-to-child transmission of HCV infection. *Virology* 2009; **390**: 64-70 [PMID: 19481774 DOI: 10.1016/j.virol.2009.05.007]

84 **Martinetti M**, Pacati I, Cuccia M, Badulli C, Pasi A, Salvaneschi L, Minola E, De Silvestri A, Iannone AM, Maccabruni A. Hierarchy of baby-linked immunogenetic risk factors in the vertical transmission of hepatitis C virus. *Int J Immunopathol Pharmacol* 2006; **19**: 369-378 [PMID: 16831303]

85 **Resti M**, Azzari C, Galli L, Zuin G, Giacchino R, Bortolotti F, Marcellini M, Moriondo M, de Martino M, Vierucci A. Maternal drug use is a preeminent risk factor for mother-to-child hepatitis C virus transmission: results from a multicenter study of 1372 mother-infant pairs. *J Infect Dis* 2002; **185**: 567-572 [PMID: 11865412 DOI: 10.1086/339013]

86 **Syriopoulou V**, Nikolopoulou G, Daikos GL, Theodoridou M, Pavlopoulou I, Nicolaidou P, Manolaki N. Mother to child transmission of hepatitis C virus: rate of infection and risk factors. *Scand J Infect Dis* 2005; **37**: 350-353 [PMID: 16051571 DOI: 10.1080/00365540510032105]

87 **Dowd KA**, Hershow RC, Yawetz S, Larussa P, Diaz C, Landesman SH, Paul ME, Read JS, Lu M, Thomas DL, Netski DM, Ray SC. Maternal neutralizing antibody and transmission of hepatitis C virus to infants. *J Infect Dis* 2008; **198**: 1651-1655 [PMID: 18928374 DOI: 10.1086/593067]

88 **Meunier JC**, Bukh J, Diaz G, Tovo PA, Casadei AM, Quinti I, Iorio R, Emerson S, Purcell RH, Farci P. Neutralizing antibodies to hepatitis C virus in perinatally infected children followed up prospectively. *J Infect Dis* 2011; **204**: 1741-1745 [PMID: 22006993 DOI: 10.1093/infdis/jir631]

89 **Granovsky MO**, Minkoff HL, Tess BH, Waters D, Hatzakis A, Devoid DE, Landesman SH, Rubinstein A, Di Bisceglie AM, Goedert JJ. Hepatitis C virus infection in the mothers and infants cohort study. *Pediatrics* 1998; **102**: 355-359 [PMID: 9685438]

90 **European Collaborative Study**. Gender and race do not alter early-life determinants of clinical disease progression in HIV-1 vertically infected children. *AIDS* 2004; **18**: 509-516 [PMID: 15090804]

91 **Galli L**, Puliti D, Chiappini E, Gabiano C, Tovo PA, Pezzotti P, de Martino M. Lower mother-to-child HIV-1 transmission in boys is independent of type of delivery and antiretroviral prophylaxis: the Italian Register for HIV Infection in Children. *J Acquir Immune Defic Syndr* 2005; **40**: 479-485 [PMID: 16280705]

92 **Ureta-Vidal A**, Angelin-Duclos C, Tortevoye P, Murphy E, Lepère JF, Buigues RP, Jolly N, Joubert M, Carles G, Pouliquen JF, de Thé G, Moreau JP, Gessain A. Mother-to-child transmission of human T-cell-leukemia/lymphoma virus type I: implication of high antiviral antibody titer and high proviral load in carrier mothers. *Int J Cancer* 1999; **82**: 832-836 [PMID: 10446450 DOI: 10.1002/(SICI)1097-0215(19990909)82:6]

93 **Palomba E**, Manzini P, Fiammengo P, Maderni P, Saracco G, Tovo PA. Natural history of perinatal hepatitis C virus infection. *Clin Infect Dis* 1996; **23**: 47-50 [PMID: 8816128 DOI: 10.1093/clinids/23.1.47]

94 **Tovo PA**, Pembrey LJ, Newell ML. Persistence rate and progression of vertically acquired hepatitis C infection. European Paediatric Hepatitis C Virus Infection. *J Infect Dis* 2000; **181**: 419-424 [PMID: 10669321 DOI: 10.1086/315264]

95 **Resti M**, Jara P, Hierro L, Azzari C, Giacchino R, Zuin G, Zancan L, Pedditzi S, Bortolotti F. Clinical features and progression of perinatally acquired hepatitis C virus infection. *J Med Virol* 2003; **70**: 373-377 [PMID: 12766999 DOI: 10.1002/jmv.1040]

96 **Jonas MM**. Children with hepatitis C. *Hepatology* 2002; **36**: S173-S178 [PMID: 12407591 DOI: 10.1002/hep.1840360722]

97 **Marchant A**, Appay V, Van Der Sande M, Dulphy N, Liesnard C, Kidd M, Kaye S, Ojuola O, Gillespie GM, Vargas Cuero AL, Cerundolo V, Callan M, McAdam KP, Rowland-Jones SL, Donner C, McMichael AJ, Whittle H. Mature CD8(+) T lymphocyte response to viral infection during fetal life. *J Clin Invest* 2003; **111**: 1747-1755 [PMID: 12782677 DOI: 10.1172/JCI200317470]

98 **Babik JM**, Cohan D, Monto A, Hartigan-O'Connor DJ, McCune JM. The human fetal immune response to hepatitis C virus exposure in utero. *J Infect Dis* 2011; **203**: 196-206 [PMID: 21288819 DOI: 10.1093/infdis/jiq044]

99 **European Paediatric Hepatitis C Virus Network**. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clin Infect Dis* 2005; **41**: 45-51 [PMID: 15937762 DOI: 10.1086/430601]

100 **Yeung LT**, To T, King SM, Roberts EA. Spontaneous clearance of childhood hepatitis C virus infection. *J Viral Hepat* 2007; **14**: 797-805 [PMID: 17927616 DOI: 10.1111/j.1365-2893.2007.00873.x]

101 **Bortolotti F**, Verucchi G, Cammà C, Cabibbo G, Zancan L, Indolfi G, Giacchino R, Marcellini M, Marazzi MG, Barbera C, Maggiore G, Vajro P, Bartolacci S, Balli F, Maccabruni A, Guido M. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology* 2008; **134**: 1900-1907 [PMID: 18439604 DOI: 10.1053/j.gastro.2008.02.082]

102 **Abdel-Hady M**, Bunn SK, Sira J, Brown RM, Brundler MA, Davies P, Kelly DA. Chronic hepatitis C in children--review of natural history at a National Centre. *J Viral Hepat* 2011; **18**: e535-e540 [PMID: 21914074 DOI: 10.1111/j.1365-2893.2011.01456.x]

103 **Farmand S**, Wirth S, Löffler H, Woltering T, Kenzel S, Lainka E, Henneke P. Spontaneous clearance of hepatitis C virus in vertically infected children. *Eur J Pediatr* 2012; **171**: 253-258 [PMID: 21735055 DOI: 10.1007/s00431-011-1517-3]

104 **Riche H**, Chiara Y, Jaboulay JM. [Clinical outcome in the surgery of intracranial aneurysms: 229 cases]. *Agressologie* 1990; **31**: 271-273 [PMID: 2288341 DOI: 10.1016/j.jpeds.2012.06.057]

105 **Indolfi G**, Mangone G, Calvo PL, Bartolini E, Regoli M, Serranti D, Calitri C, Tovo PA, de Martino M, Azzari C, Resti M. Interleukin 28B rs12979860 single-nucleotide polymorphism predicts spontaneous clearance of hepatitis C virus in children. *J Pediatr Gastroenterol Nutr* 2014; **58**: 666-668 [PMID: 24792632 DOI: 10.1097/MPG.0000000000000275]

106 **Indolfi G**, Mangone G, Bartolini E, Nebbia G, Calvo PL, Moriondo M, Tovo PA, de Martino M, Azzari C, Resti M. Comparative analysis of rs12979860 SNP of the IFNL3 gene in children with hepatitis C and ethnic matched controls using 1000 Genomes Project data. *PLoS One* 2014; **9**: e85899 [PMID: 24465773 DOI: 10.1371/journal.pone.0085899]

107 **Mack CL**, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA, Rosenthal P, Schwarz KB. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. *J Pediatr Gastroenterol Nutr* 2012; **54**: 838-855 [PMID: 22487950 DOI: 10.1097/MPG.0b013e318258328d]

108 **González-Peralta RP**, Langham MR, Andres JM, Mohan P, Colombani PM, Alford MK, Schwarz KB. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. *J Pediatr Gastroenterol Nutr* 2009; **48**: 630-635 [PMID: 19412012 DOI: 10.1097/MPG.0b013e318170af04]

109 **England K**, Pembrey L, Tovo PA, Newell ML. Growth in the first 5 years of life is unaffected in children with perinatally-acquired hepatitis C infection. *J Pediatr* 2005; **147**: 227-232 [PMID: 16126055 DOI: 10.1016/j.jpeds.2005.04.010]

110 **Pembrey L**, Newell ML, Tovo PA. Age-related lymphocyte and neutrophil levels in children of hepatitis C-infected women. *Pediatr Infect Dis J* 2008; **27**: 800-807 [PMID: 18664931 DOI: 10.1097/INF.0b013e31816ffc0e]

111 **Kage M**, Fujisawa T, Shiraki K, Tanaka T, Fujisawa T, Kimura A, Shimamatsu K, Nakashima E, Kojiro M, Koike M, Tazawa Y, Abukawa D, Okaniwa M, Takita H, Matsui A, Hayashi T, Etou T, Terasawa S, Sugiyama K, Tajiri H, Yoden A, Kajiwara Y, Sata M, Uchimura Y. Pathology of chronic hepatitis C in children. Child Liver Study Group of Japan. *Hepatology* 1997; **26**: 771-775 [PMID: 9303511 DOI: 10.1002/hep.510260333]

112 **Badizadegan K**, Jonas MM, Ott MJ, Nelson SP, Perez-Atayde AR. Histopathology of the liver in children with chronic hepatitis C viral infection. *Hepatology* 1998; **28**: 1416-1423 [PMID: 9794930 DOI: 10.1002/hep.510280534]

113 **Mohan P**, Barton BA, Narkewicz MR, Molleston JP, Gonzalez-Peralta RP, Rosenthal P, Murray KF, Haber B, Schwarz KB, Goodman ZD. Evaluating progression of liver disease from repeat liver biopsies in children with chronic hepatitis C: a retrospective study. *Hepatology* 2013; **58**: 1580-1586 [PMID: 23703847 DOI: 10.1002/hep.26519]

114 **Larrubia JR**, Moreno-Cubero E, Lokhande MU, García-Garzón S, Lázaro A, Miquel J, Perna C, Sanz-de-Villalobos E. Adaptive immune response during hepatitis C virus infection. *World J Gastroenterol* 2014; **20**: 3418-3430 [PMID: 24707125 DOI: 10.3748/wjg.v20.i13.3418]

115 **Gismondi MI**, Becker PD, Díaz Carrasco JM, Guzmán CA, Campos RH, Preciado MV. Evolution of hepatitis C virus hypervariable region 1 in immunocompetent children born to HCV-infected mothers. *J Viral Hepat* 2009; **16**: 332-339 [PMID: 19228286 DOI: 10.1111/j.1365-2893.2009.01071.x]

116 **Gaud U**, Langer B, Petropoulou T, Thomas HC, Karayiannis P. Changes in hypervariable region 1 of the envelope 2 glycoprotein of hepatitis C virus in children and adults with humoral immune defects. *J Med Virol* 2003; **69**: 350-356 [PMID: 12526045 DOI: 10.1002/jmv.10296]

117 **Canobio S**, Guilbert CM, Troesch M, Samson J, Lemay M, Pelletier VA, Bernard-Bonnin AC, Kozielski R, Lapointe N, Martin SR, Soudeyns H. Differing patterns of liver disease progression and hepatitis C virus (HCV) quasispecies evolution in children vertically coinfected with HCV and human immunodeficiency virus type 1. *J Clin Microbiol* 2004; **42**: 4365-4369 [PMID: 15365046 DOI: 10.1128/JCM.42.9.4365-4369.2004.120]

118 **Zignego AL**, Ferri C, Pileri SA, Caini P, Bianchi FB. Extrahepatic manifestations of Hepatitis C Virus infection: a general overview and guidelines for a clinical approach. *Dig Liver Dis* 2007; **39**: 2-17 [PMID: 16884964 DOI: 10.1016/j.dld.2006.06.008]

119 **Matsumoto S**, Nakajima S, Nakamura K, Etani Y, Hirai H, Shimizu N, Yokoyama H, Kobayashi Y, Tajiri H, Shima M, Okada S. Interferon treatment on glomerulonephritis associated with hepatitis C virus. *Pediatr Nephrol* 2000; **15**: 271-273 [PMID: 11149124]

120 **Sugiura T**, Yamada T, Kimpara Y, Fujita N, Goto K, Koyama N. Effects of pegylated interferon alpha-2a on hepatitis-C-virus-associated glomerulonephritis. *Pediatr Nephrol* 2009; **24**: 199-202 [PMID: 18696119 DOI: 10.1007/s00467-008-0948-1]

121 **Gregorio GV**, Pensati P, Iorio R, Vegnente A, Mieli-Vergani G, Vergani D. Autoantibody prevalence in children with liver disease due to chronic hepatitis C virus (HCV) infection. *Clin Exp Immunol* 1998; **112**: 471-476 [PMID: 9649217 DOI: 10.1046/j.1365-2249.1998.00574.x]

122 **Muratori P**, Muratori L, Verucchi G, Attard L, Bianchi FB, Lenzi M. Non-organ-specific autoantibodies in children with chronic hepatitis C: clinical significance and impact on interferon treatment. *Clin Infect Dis* 2003; **37**: 1320-1326 [PMID: 14583865 DOI: 10.1086/379018]

123 **Gehring S**, Kullmer U, Koeppelmann S, Gerner P, Wintermeyer P, Wirth S. Prevalence of autoantibodies and the risk of autoimmune thyroid disease in children with chronic hepatitis C virus infection treated with interferon-alpha. *World J Gastroenterol* 2006; **12**: 5787-5792 [PMID: 17007043 DOI: 10.3748/wjg.v12.i36.5787]

124 **Bortolotti F**, Muratori L, Jara P, Hierro L, Verucchi G, Giacchino R, Barbera C, Zancan L, Guido M, Resti M, Pedditzi S, Bianchi F, Gatta A. Hepatitis C virus infection associated with liver-kidney microsomal antibody type 1 (LKM1) autoantibodies in children. *J Pediatr* 2003; **142**: 185-190 [PMID: 12584542 DOI: 10.1067/mpd.2003.45]

125 **Stroffolini T**, Colloredo G, Gaeta GB, Sonzogni A, Angeletti S, Marignani M, Pasquale G, Venezia G, Craxì A, Almasio P. Does an 'autoimmune' profile affect the clinical profile of chronic hepatitis C? An Italian multicentre survey. *J Viral Hepat* 2004; **11**: 257-262 [PMID: 15117328 DOI: 10.1111/j.1365-2893.2004.00489.x]

126 **Indolfi G**, Bartolini E, Olivito B, Azzari C, Resti M. Autoimmunity and extrahepatic manifestations in treatment-naïve children with chronic hepatitis C virus infection. *Clin Dev Immunol* 2012; **2012**: 785627 [PMID: 226456232012 DOI: 10.1155/2012/785627]

127 **Bretting H**, Jacobs G, Müller S, Breitfeld O. The galactan-degrading enzymes in the snail Biomphalaria glabrata. *Comp Biochem Physiol B* 1991; **99**: 629-636 [PMID: 1769210 DOI: 10.1111/j.1365-2265.2007.03009.x]

128 **Pham TN**, Coffin CS, Michalak TI. Occult hepatitis C virus infection: what does it mean? *Liver Int* 2010; **30**: 502-511 [PMID: 20070513 DOI: 10.1111/j.1478-3231.2009.02193.x]

131 **Vidimliski PD**, Nikolov I, Geshkovska NM, Dimovski A, Rostaing L, Sikole A. Review: Occult hepatitis C virus infection: still remains a controversy. *J Med Virol* 2014; **86**: 1491-1498 [PMID: 24895180 DOI: 10.1002/jmv.23979]

130 **Larrubia JR**, Moreno-Cubero E, Miquel J, Sanz-de-Villalobos E. Hepatitis C virus-specific cytotoxic T cell response restoration after treatment-induced hepatitis C virus control. *World J Gastroenterol* 2015; **21**: 3480-3491 [PMID: 25834312 DOI: 10.3748/wjg.v21.i12.3480]

131 **Mohan P**, Chandra RS, Escolar DM, Luban NL. Inflammatory myopathy and hepatitis C in a pediatric patient: role of liver biopsy in evaluating the severity of liver disease. *Hepatology* 2001; **34**: 851-852 [PMID: 11584390 DOI: 10.1002/hep.510340439]

132 **Ertekin V**, Tan H. Opsoclonus-myoclonus syndrome attributable to hepatitis C infection. *Pediatr Neurol* 2010; **42**: 441-442 [PMID: 20472199 DOI: 10.1016/j.pediatrneurol.2010.02.009]

133 **Barth H**. Hepatitis C virus: Is it time to say goodbye yet? Perspectives and challenges for the next decade. *World J Hepatol* 2015; **7**: 725-737 [PMID: 25914773 DOI: 10.4254/wjh.v7.i5.725]

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