

## REVIEW

# Perinatal hepatitis C virus infection: diagnosis and management

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Hepatitis C virus (HCV) infection in children is becoming an increasing challenge to health professionals. As our understanding of the disease evolves, so must our diagnostic and management strategies. In the 1990s, when HCV testing became available, children identified with HCV infection in the UK were mostly those who had required blood products, particularly those with haematological disorders. Acquiring knowledge of the natural history of HCV infection was confounded by the co-morbidity of iron overload, viral co-infection, and chemotherapy.

More than a decade later, we face different challenges. Most children now diagnosed with HCV have vertically acquired infection and no co-morbidity. Are there sufficient advantages to diagnosis to make screening at-risk infants worthwhile? Has our understanding of the natural history advanced? With improved antiviral strategies, when should treatment be considered? This paper aims to review our current understanding of vertically acquired HCV transmission, and give recommendations for investigation and management.

## Prevalence

The prevalence of chronic HCV infection in the UK is estimated at 0.4%, with most infected individuals unaware of their HCV status.<sup>1</sup> HCV has been classified into six major genetic types (genotypes 1–6) with some genotypes also having subtypes a and b. In England and Wales the most prevalent genotypes are 1a and 1b (47%) and 3a (37%).<sup>2</sup> The prevalence in children is not known. During active surveillance by the British Paediatric Surveillance Unit (BPSU) in 1997 and 1998, 182 infected children were identified, most of whom were infected by blood products.<sup>3</sup> Now, most infected children are those born to HCV positive mothers, as demonstrated by studies in the UK and Italy.<sup>4, 5</sup>

It is difficult to estimate the potential extent of the problem in children as antenatal screening of women is selective and so is not representative. Maternal intravenous drug use (IVDU) is the major risk factor for HCV infection. Although the UK National Screening Committee recommends that women with a history of intravenous drug use are offered screening, routine antenatal testing is *not* currently recommended.<sup>6</sup> The rationale supporting this recommendation is that there are currently no interventions of proven

safety and efficacy for prevention of mother-to-child transmission, and furthermore the long term natural history of vertically acquired HCV infection has not been adequately described. Nevertheless, in the UK, regional prevalence rates in pregnant women, estimated in the Northern and Yorkshire Region, North Thames, and London by anonymised screening, ranged from 0.19% to 0.43%,<sup>7, 8</sup> leading to an estimated UK seroprevalence of 0.16%.<sup>7</sup> The anonymised testing was performed on neonatal<sup>7</sup> or maternal<sup>8</sup> blood samples. In an inner city area of London, where 98% of women attending for antenatal care accepted testing, anti HCV seroprevalence was 0.8%;<sup>9</sup> history of IVDU use was apparent in 40% of those who were HCV positive. In Scotland, an area with a high rate of IVDU, the estimated national maternal anti-HCV seroprevalence was 0.29–0.4%.<sup>10</sup> In less than half (46%) the diagnosis had already been made as the presence of risk factors for HCV had been identified, and in only 24% of infected women was the diagnosis made prior to pregnancy. These studies confirm that in women, as in the general population, HCV infection is often unsuspected and undiagnosed, and thus perinatal transmission may be undetected. It is estimated that 1150 pregnancies annually in the UK would involve a woman infected with HCV, leading to approximately 70 infected infants being born each year.<sup>7</sup>

## RISK OF TRANSMISSION

Vertical transmission is almost always confined to women who have detectable HCV RNA.<sup>11–14</sup> There is an extremely low risk of transmission if HCV RNA is not detected,<sup>11</sup> despite occasional reports of HCV RNA negative women transmitting infection.<sup>15–17</sup> Risk of transmission is increased by level of maternal HCV viraemia and maternal HIV co-infection.<sup>18</sup> Maternal IVDU has also been suggested as an independent factor increasing transmission,<sup>19</sup> but not confirmed in other studies. A recent study reported that female infants were twice as likely to be infected as males.<sup>17</sup> In a systematic review of 77 studies published between 1992 and 2000, rate of vertical transmission of HCV from women with HIV infection was 22.1% and without HIV infection was 4.3%.<sup>18</sup> In a European study of 1474 HCV infected women, rates of transmission with and without HIV infection were 13.9% and 6.6% respectively.<sup>20</sup>

Both intrauterine and perinatal transmission are important routes of vertical infection. The mode of delivery does not affect risk of transmission, with similar rates of infection in infants

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delivered by caesarean section or vaginally,<sup>12 18 20–24</sup> unless the mother is co-infected with HIV when delivery by caesarean section may have a protective effect.<sup>20</sup> The potential benefit of elective caesarean section with membranes intact is suggested by one small study,<sup>21</sup> and if confirmed, would support the case for antenatal screening. In a recent study, membrane rupture of longer than 6 hours before delivery and internal fetal monitoring were both associated with an increased risk of transmission.<sup>25</sup> Although HCV RNA may be detected in breast milk and colostrum,<sup>26</sup> breast feeding does not appear to increase the rate of HCV transmission<sup>12 18 20–22 26</sup> unless the mother is also HIV positive.<sup>20</sup> Current recommendations are that women with HCV *without* HIV co-infection can be advised to breast feed.

### TIMING AND DIAGNOSIS OF HCV TRANSMISSION

The diagnosis of perinatal transmission is confused by passive transfer of maternal antibody up to 13 months and occasionally 18 months, meaning that anti-HCV testing is of limited value in infancy.<sup>21 27</sup> Infants are considered infected if HCV RNA is positive on two or more occasions. In a European study, 31% of infected infants screened had detectable HCV RNA as early as three days of age, suggesting intrauterine infection.<sup>24</sup> However, in most, HCV RNA only reaches detectable levels after several weeks, in keeping with perinatal rather than intrauterine acquisition. Sensitivity of PCR for diagnosis increases with time due to levels of HCV RNA gradually rising to reach the threshold of detection.<sup>12 21 23 27–29</sup> Sensitivity has been estimated as 22% at age less than 1 month and 97% at greater than 1 month.<sup>21 27</sup>

Although there is agreement that testing should be delayed to at least 4 weeks of age, some recommend waiting until 3 months.<sup>30</sup> A practical recommendation is to delay testing until at least 8 weeks, which could coincide with routine childhood immunisation.

Chronic infection is defined as the persistence of HCV RNA for at least six months and resolution is determined by the disappearance of HCV RNA. In perinatally infected infants, loss of HCV RNA may reflect transient viraemia or resolved infection, but there is probably no clinical significance in making the distinction.

### NATURAL HISTORY

Natural history may be explored in terms of spontaneous resolution, symptoms and signs of liver disease, and histological progression. Spontaneous resolution is defined by sustained disappearance of HCV RNA from the serum, accompanied by normalisation of aminotransferase enzymes, although anti-HCV antibody may persist. Caution must still be used however in defining disappearance of HCV RNA from serum as a “cure”: low levels of HCV RNA, of uncertain clinical significance may persist below the conventional threshold of detection.<sup>31 32</sup>

It is estimated that 75% of adults infected with HCV develop chronic infection, with an increased lifetime risk of cirrhosis and hepatocellular carcinoma.<sup>33</sup> Adverse prognostic factors include older age at acquisition of infection: acquiring HCV infection at age >40 years has a 20% risk of cirrhosis within 20 years, compared to <10% if age <40. Individuals with consistently normal ALT levels appear to have slower progression of fibrosis, but hepatitis C genotype has no effect on severity or progression.<sup>33–35</sup> There is evidence that some populations may have a more favourable outcome: for example, of 1980 women acquiring HCV from anti-D immunoglobulin, only 46% remained HCV RNA positive after 25 years, and only 0.5% developed cirrhosis.<sup>36</sup> Presence of co-infection, alcoholic liver disease, and male gender also adversely affect prognosis.

Studies of natural history in children often combine cohorts with both vertical and horizontal transmission, and a wide range of co-morbidity and age at acquisition. Caution must be exercised when extrapolating outcomes from these studies to a different population, such as those with vertical infection and no co-morbidity.

Spontaneous resolution in children appears to be infrequent: in three large series, (including vertical and horizontal acquisition) spontaneous clearance occurred in 5.6–10%.<sup>16 37 38</sup> In the largest of these series,<sup>38</sup> children infected with genotype 3 (81% of whom were vertically infected) had the highest rate of spontaneous viral clearance (22%) when compared to other genotypes. In four long term follow up studies of children or neonates acquiring HCV by blood transfusion, spontaneous resolution occurred in 27–48% after 6–35 years.<sup>39–42</sup> In children with vertical infection, clearance rates are very variable ranging from 10% to 55%.<sup>16 22 37 40 43–46</sup> Most are small studies of 10–20 children. In the largest study, of 266 infants, approximately 20% appeared to clear infection, as determined by HCV RNA becoming negative.<sup>46</sup> Of these, 81% (26 of 32) became anti-HCV negative. It is not clear whether infection during infancy is associated with poorer clearance rates due to immune tolerance, or whether other factors such as genotype and viral load are important in influencing resolution. However, it does appear that children with transfusion acquired infection have a higher chance of spontaneous resolution than those with vertical infection.

Most children with HCV infection are asymptomatic, with minor abnormalities such as hepatomegaly or mild non-specific symptoms occasionally reported.<sup>3 16 37 38 40 44 46 47</sup> Despite this, most perinatally infected infants will have intermittently or persistently abnormal liver enzymes (AST/ALT),<sup>14 37 40 43 44 46–48</sup> particularly in the first two years of life. ALT elevation does not correlate well with histological severity.<sup>14 49</sup>

Liver biopsy has only been performed in the minority of children with HCV infection, for example in 29% of children identified by the BPSU study.<sup>3</sup> Liver biopsy is more likely to be performed in those with persistent liver dysfunction or with co-morbidity, and therefore the reported features and severity may not accurately reflect the histological spectrum. Even in the absence of symptoms and signs there may be histological evidence of chronic inflammation. Fibrosis is slowly progressive, and thus severity relates to duration of infection.<sup>23 49 50</sup> In one study of 112 children with abnormal liver enzymes, fibrosis was seen in 78%, including all children infected for more than 15 years, but was usually mild. Severe fibrosis was unusual after infection of less than 10 years' duration. Progression of fibrosis with time does not appear to be linear, and thus severity of fibrosis is not a reliable prognostic indicator.<sup>50</sup> Two studies report long term histological outcome following childhood infection and suggest a benign course.<sup>39 42</sup> Of 11 infected through neonatal blood transfusion who underwent liver biopsy after 35 years, most had mild disease, two had marked fibrosis, but none had cirrhosis;<sup>42</sup> and of 17 infected following cardiac surgery, after a mean of 19.8 years, progressive liver damage was only seen in those with co-morbidity.<sup>39</sup> In children with *vertical* HCV infection who have undergone liver biopsy, the histological spectrum reported is usually mild.<sup>16 18 43</sup> There are however reports of perinatally acquired HCV causing symptomatic liver disease and decompensated cirrhosis in young children.<sup>51 52</sup> Factors responsible for such rapid progression in the absence of co-morbidity are not known.

### ANTIVIRAL THERAPY

The aim of treatment is to achieve a sustained viral response (SVR): HCV RNA becoming undetectable and remaining so after treatment has been completed. Treatment of adults has

been shown to reduce both the rate of progression of fibrosis and the incidence of hepatocellular carcinoma and also improve the health related quality of life (HRQOL).<sup>53</sup> Current guidelines from the National Institute of Clinical Excellence recommend combination therapy with pegylated interferon and ribavirin for HCV infected adults who have evidence of chronic inflammation. The likelihood of SVR is clearly influenced by HCV genotype, with 2 and 3 having the highest rates (76%) and genotype 1 the lowest (46%).<sup>54</sup> The benefit of pegylated interferon over conventional interferon is a once rather than thrice weekly injection schedule and superior response rates, but side effects are similar including anorexia, malaise, mood disturbance, and haematological disorders.

There is currently no licensed treatment for children with HCV infection. Evolution of anti-HCV strategies has followed that in adults. A meta-analysis of interferon monotherapy reported a rate of SVR of 36% (120/366) of treated children (27% genotype 1; 70% other genotypes).<sup>55</sup> Combination therapy with ribavirin and interferon in children, reported in small studies (n = 12,<sup>56</sup> n = 41,<sup>57</sup> n = 118<sup>58</sup>) is associated with a better response rate, with SVR occurring in 46–61% (36–53% genotype 1; 84–100% genotype 2 or 3). However, side effects are common and sometimes severe. In a study of 118 children (54% vertically infected), treatment was discontinued in 7% due to adverse events.<sup>58</sup> Flu-like symptoms and neutropenia were common, neutropenia being severe in 19%. Neuropsychiatric disturbances including irritability, insomnia, and somnolence occurred in 50% and depression in 13%; four children had suicidal ideation. Pre-existing mood disturbance and treatment during adolescence were considered likely risk factors.

In a pilot study of pegylated interferon and ribavirin in 41 children, 61% were HCV RNA negative at the end of treatment,<sup>59</sup> and 67% (14/21) of children with vertical infection responded. Overall response rate was superior in genotype 2 or 3 (100%) compared with genotype 1 (53%). Temporary mood swings occurred in 15%, 82% had a flu-like illness, 75% leucopenia, 15% hair loss, and 13% redness at injection site. A randomised multicentre European study of this combination therapy is in progress.

## MANAGEMENT RECOMMENDATIONS

### Who and how to test

At-risk infants may be identified by a wide range of professionals including midwives and obstetricians as well as paediatricians in hospitals and the community. Counselling of the family should begin at the time of antenatal testing and continue at each stage of diagnosis. An algorithm for diagnosis is given in fig 1.

After diagnosis of an infant, counselling regarding natural history, treatment options, infectivity, and confidentiality must be adapted to account for the changing needs of the family during the child's infancy, childhood, and adolescence. In adults, it has been demonstrated that HRQOL may be enhanced by improving patients' understanding of HCV disease.<sup>60</sup>

### Follow up and management of children with HCV infection

It is recommended that a paediatric hepatologist is involved at an early stage: monitoring disease progression and complications, assessment of liver histology, and timely intervention with the most appropriate antiviral strategy fall within their remit. The National Specialist Commissioning Advisory Group (NSCAG) of the Department of Health fund the three supraregional paediatric hepatology centres to provide this service. Children with HCV should be reviewed six monthly to include assessment of liver function and viral status, and discuss the role of antiviral treatment. An annual

ultrasound and alpha-fetoprotein estimation is recommended, to facilitate early diagnosis of progression of liver disease or emergence of hepatocellular carcinoma. Children with HCV should be immunised against hepatitis A and B.

Ongoing shared care will be tailored according to local and regional services, which may include consultants in paediatric infectious diseases and paediatric gastroenterology. Considerable child and family support is needed to address the difficult issues of confidentiality and school notification, and strategies to reduce transmission risk while avoiding risk of stigmatisation. A specialist liaison nurse, working with community healthcare professionals is invaluable. In addition, professionals in drug addiction, local and community paediatricians, and social workers are often in the best position to provide support for the whole family, and encourage compliance.

### Therapy for HCV infection in children

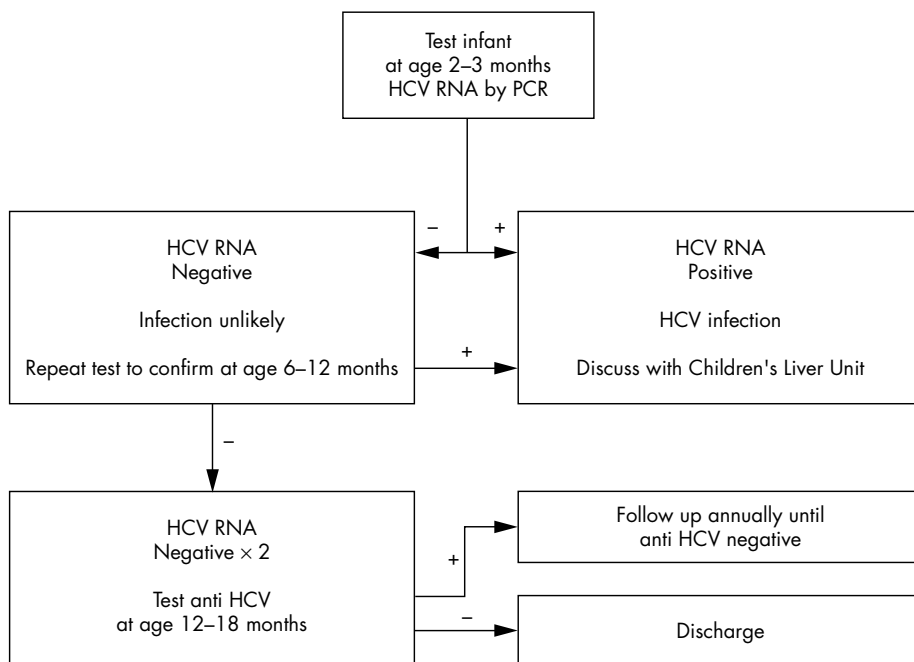
Who and when to treat is a topic that is controversial and continues to evolve as antiviral strategies improve. It could be argued that all children should be treated; factors favouring treatment response, including absence of cirrhosis, young age at acquisition, and absence of co-morbidity are often present, and children tolerate treatment better than adults. Furthermore, there is some evidence that treatment after a short duration of infection increases the likelihood of response.<sup>61</sup> However, children usually remain asymptomatic during childhood and histological progression is expected to be slow. Interferon is not recommended for children under 2 years of age, and with the increased possibility of spontaneous seroconversion occurring within the first three years of life, treatment should be delayed at least until age 3 years or older. Treatment could therefore be deferred to adulthood and only commenced in the presence of progressing disease: this strategy, however, allows the infectivity of the child to continue, and the stigma of HCV infection to remain. The possibility of treatment should be discussed with all families. It is reasonable either to instigate or defer treatment, depending on the clinical and social context.

With current evidence of good response, children with genotype 2 or 3 are the group most likely to benefit from treatment. Potential side effects must be fully explained, and any additional risk factors identified. Treating in the presence of psychological ill health (unrelated to HCV) and during adolescence may be best avoided, but are not absolute contraindications. Younger children however do appear to tolerate treatment better. For genotype 1, the benefit/risk argument is not as strongly in favour of treatment, although 50% will respond.

Treatment should be offered by teams with experience in using combination therapy, as monitoring of side effects and providing support is essential. Standardised protocols should be followed whether or not the treatment is part of a clinical trial.

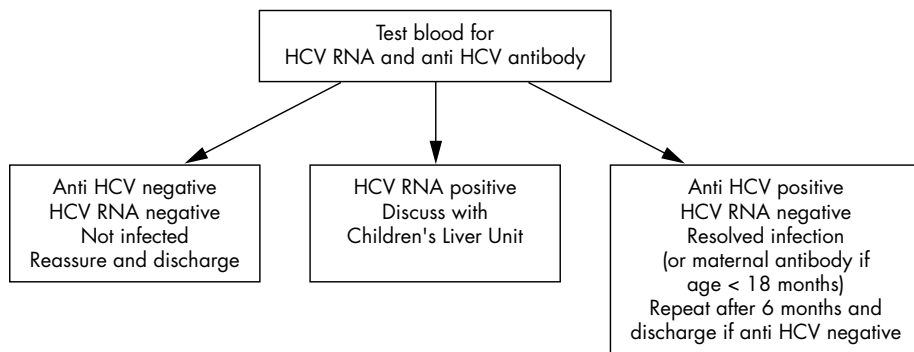
Clinical guidelines on the management of hepatitis C in adults have been compiled on behalf of the Royal College of Physicians of London and the British Society of Gastroenterology. They state: "Patients infected with hepatitis C virus (HCV) should be referred to a clinician with a particular interest in the infection. Patients must have access to adequate counselling from a health carer with a knowledge and experience of chronic HCV infection. All patients must have access to the appropriate diagnostic and therapeutic options...".<sup>62</sup> During the BPSU survey, 54 centres notified patients, with 34 centres reporting one child each, and eight paediatric specialties were represented. This was understandable, reflecting the pattern of HCV infection at that time: children with HCV usually had another underlying disorder requiring specialist care. Furthermore, significance

1. Mother: Anti HCV positive and/or HCV RNA positive



**Figure 1** Algorithm for diagnosis of HCV infection in infants at risk of perinatal infection.

2. Child referred for diagnosis at age 12 months or older



of infection and natural history were uncertain, rationale for antiviral treatment unclear, and benefits of referral not apparent. Our current knowledge has changed this situation.

**THE FUTURE**

It is anticipated that our knowledge of the natural history of vertical infection will continue to increase with time. In the UK a National HCV register<sup>63</sup> collates data from adults and children with known date and route of HCV acquisition. Initial data sources for children were the UK “look back” identification of recipients of infected blood products and the BPSU surveillance study. The ongoing prospective data collection now incorporates children referred for registration from the three paediatric supraregional liver centres in Birmingham, London, and Leeds. This register should provide a valuable resource for documenting the natural history and informing future management and treatment decisions.

The Department of Health, in its strategy for hepatitis C, aims to raise awareness and encourage testing in those at risk. If successfully implemented, more children at risk of HCV infection will be identified, and therefore referral for

appropriate management facilitated. Managing children with HCV infection will continue to depend on a coordinated approach from all healthcare professionals involved with women and children.

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