original paper

Outcome of infants born to hepatitis C infected women

CM Healy[1,4], MT Cafferkey[1,4,7], A Conroy[6], S Dooley[6], WW Hall[6], M Beckett[1], TA Clarke[1,4,7], MJ White[2,5], WA Gorman[3,5], KM Butler[1,4,5]

Rotunda Hospital[1], Coombe Women's Hospital[2], National Maternity Hospital, Holles Street[3], The Children's Hospital, Temple Street[4], Our Lady's Hospital for Sick Children, Crumlin[5], Virus Reference Laboratory[6], University College Dublin, Royal College of Surgeons of Ireland[7], Dublin, Ireland.

Abstract

Background Hepatitis C virus (HCV) can be transmitted vertically from mother to infant, either late in pregnancy or at delivery.

Aims To determine the outcome of infants born to HCV infected women, to characterise epidemiology and to design an appropriate infant monitoring schedule.

Methods Three hundred and fourteen infants, born to 296 HCV positive women between 1994 and 1999 were monitored for a median of 18 months (range 1-52).

Results Forty per cent of infants were small for age and 46% had neonatal abstinence syndrome (NAS). Of 173 infants of defined status, 11 were infected (vertical transmission rate [VTR] 6.4%, 95% CI 2.8-10). Infected infants were diagnosed at a median of three months (range 0.5-10). Liver transaminases elevation was documented in 8% of uninfected infants. A negative HCV PCR test before one month of age did not exclude infection but all infected patients had detectable HCV RNA when next tested (range 2-10 months).

Conclusions 94% of infants born to HCV antibody positive women are not HIV infected. Liver transaminase elevation in exposed infants is not always indicative of infection. A minimum monitoring schedule of testing (PCR and antibody) at six to eight weeks, six and 18 months allows early diagnosis while detecting late seroconversions.

Introduction

HCV can be transmitted vertically from mother to infant, either late in pregnancy or at delivery. HCV vertical transmission rates have varied in reported studies; in the absence of maternal HIV, infection rates are of the order of 5-10%.[1-10] HCV RNA has also been found in breast milk, the significance of which is uncertain.[11] Given increasing detection rates of HCV in Irish antenatal clinics[12] clarification of infant outcome and the design of an appropriate monitoring schedule, to minimise infant venepuncture and clinic visits without compromising reliable early diagnosis is now essential.

This study aimed to define the outcome of infants born to HCV infected women, to characterise the epidemiology and risk factors for vertically transmitted HCV, to ascertain VTR, to determine the age of seroreversion in uninfected children, and the age of diagnosis and early clinical course in infected infants. Taking these factors into account, a monitoring schedule for infants born to HCV infected women is proposed.

Methods

Selective screening for HCV infection in pregnant women takes place in each of the three main Dublin maternity hospitals.[12] After birth, infants of HCV positive mothers are referred to the paediatric infectious diseases service at one of two children's hospitals. Prospective observational monitoring of all such referrals was initiated in January 1994. Data gathered included maternal demographics, risk factors for HCV acquisition, obstetric and perinatal history and the infant's clinical course and outcome. Where necessary, data was supplemented by retrospective chart review.

In keeping with current standard practice, blood from the umbilical cord or an infant sample was tested for hepatitis C antibody to confirm perinatal risk. Infant clinical and virologic evaluations were scheduled every four to six months until 18 months of age. All serological and molecular testing of mothers and infants was performed at the Virus Reference Laboratory, University College Dublin. Hepatitis C antibody was detected using one or more commercial third generation enzyme immunoassays (Ortho, Abbott Axysm). Confirmation of antibody status was determined using the RIBA-3 assay. Hepatitis C RNA was detected using the Amplicor HCV assay (Roche) and an in-house RT-PCR assay (detects >100 copies/ml). Viral load, when available, was measured by branched DNA signal amplification (Chiron) and HCV genotype was identified by restriction fragment length polymorphism (RFLP).[13]

Infants were classified into three subgroups defined by their laboratory data. Infected infants had a positive antibody test and detectable viraemia by PCR on two specimens taken two months apart after one week of age or were persistently hepatitis C antibody positive after 18 months of age. Infants who were antibody negative at 18 months of age or had at least one negative antibody test and two separate negative PCR tests taken two months apart (the second at or after six months of age) were deemed uninfected. All remaining HCV antibody positive infants were considered to be of indeterminate status.

The age at seroreversion was defined as the midpoint between the age at last positive and first negative antibody test.

The Ghent formula was used to calculate the VTR.[14] This provides two estimates for transmission. The first assumes that all patients of indeterminate status, who have died or been lost to follow up are uninfected and therefore provides an estimate of the minimum transmission occurring. An intermediate estimate of the VTR is derived based only on those patients of defined status. Baseline characteristics among transmitters and nontransmitters were compared using the chi-square and Fisher exact tests.

Results

Patient population

Three hundred and fourteen infants were born to 296 HCV infected mothers. The maternal population has been previously described[12] and is summarised in Table 1.

Table 1. Maternal demographics and risk factors for infection

Age at delivery (years)	
Median (range)	24 (16-41)
Nationality	No (%)
Irish	289 (97)
African	6 (2)
Eastern European	1 (<1)
Risk factors for infection	
IVDU	244 (83)
Heterosexual exposure	25 (8)
Infected blood products	16 (5.5)
Tattoos	2 (<1)
No risk identified	9 (3)

Infant characteristics and outcome

One hundred and sixty-five male and 149 female infants were prospectively monitored from birth. The median gestation was 39 weeks (range 27-43 weeks) and median birth weight 2.98kg (1.3-4.84kg). Seventeen per cent were less than the 3rd centile and 40% less than the 10th centile for weight. Eight infants were breast fed. One hundred and forty-five infants (46%) developed NAS requiring treatment. Seventeen acquired unrelated perinatal infections. Congenital anomalies of varying clinical significance were detected in 13 others.

Infant deaths

There were three deaths. One premature infant with severe NAS died of profound apnoea and bradycardia at two weeks of age, one uninfected infant developed a spinal cord astrocytoma and one suffered sudden infant death syndrome (SIDS).

Infection status

The median duration of monitoring was 18 months (range 1-52 months) and median number of visits per infant is three (range 1-12). Infection status has been ascertained in 173 (11 infected, 162 uninfected), an additional 72 are >18months of age, but lost to follow up, and 69 have not had their full assessments performed and remain of indeterminate status. Four infants had HCV RNA detected on one occasion only; all subsequently tested HCV RNA-negative on at least two occasions, seroreverted and are deemed uninfected. In this study, the transmission rate calculated based only on those patients of known outcome, is 6.4% (2.8-10%, 95% CI) and the minimum VTR, i.e. where it is assumed that all of indeterminate status or lost to follow up are uninfected, is 3.5% (1.5-5.5%, 95% CI).

Infected infants

Eleven infants, 17-57 months, are HCV infected. HCV viral genotypes include five type 1a, two type 1b and four type 3. The median age at diagnosis was three months (range 2 weeks to 10 months). Six were HCV RNA-positive by three months of age, an additional four by six months and the remaining infant was positive when PCR was first obtained at 10 months of age. Four infants tested HCV RNA-negative within the first month of life, all of whom were HCV RNA-positive when next tested at eight weeks, five months (two infants) and six months of age respectively. No infant had a significant blood/bodily fluid exposure making the possibility of postnatal transmission unlikely. One infant with waning antibody at five months tested antibody negative at six months despite persistent viraemia (infant F; see Figure 1). Similarly, antibody response as evidenced by RIBA banding was noted to wane at three to six months in eight additional infected infants, and in the absence of PCR testing, could erroneously be thought to herald seroreversion.

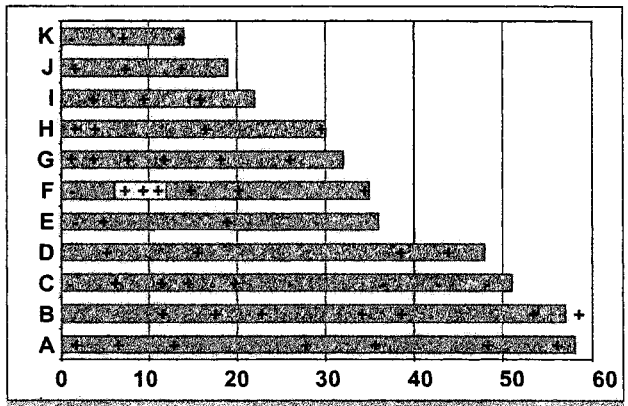

Figure 1. Antibody status (bars, shaded=positive; clear=negative)) and HCV RNA (+/-) profile of infected infants over time. Age (months at testing on x axis.

Three infants had hepatomegaly. All had elevation of liver transaminases with normal bilirubin levels (see Figure 2); viral loads varied between 200,000 and 74,450,000 genome equivalents/ml. Two infants had positive anti-smooth muscle antibodies. Patient I, clinically asymptomatic, developed an acute hepatitis at six months of age with markedly abnormal liver function (AST 498 U/L, ALT 695 U/L, gamma GT 132 U/L). Liver ultrasound was normal; serologic testing for hepatitis A and B was negative. Liver function tests are gradually improving at 18 months of age. Patient C, with viral burden of between 200,000 and 8,591,000 genome equivalents/ml on four occasions had a liver biopsy at one year of age. This showed

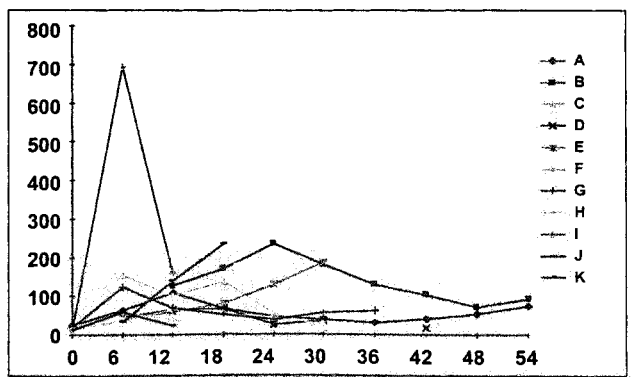

Figure 2. ALT (U/L) vs age (months)

a mixed inflammatory infiltrate, piecemeal necrosis in the liver plate regions and mild fibrosis. Treatment was planned but deferred pending foster care placement. HCV RNA spontaneously became undetectable at 27 months and he remains RNA negative with normal transaminases at 42 months of age. All infected infants have completed or are in the process of completing hepatitis A and B immunisation. No infant is HIV infected. No patient has yet received specific anti-HCV therapy.

Uninfected infants

One hundred and sixty-two infants are not infected. Forty-four per cent had seroreverted by nine months and 77% by one year of age. The median age at seroreversion is nine months (range 2.2-21.5 months). No late seroconversions have been detected in 75 infants tested at >18 months of age. Thirteen uninfected infants developed transient elevation of liver transaminases (<10 times normal) unrelated to intercurrent illness. In one infant, elevation persisted to 32 months with no cause identified despite extensive investigation and with ultimate resolution. HCV RNA was negative on multiple occasions during this period. Characteristics of infected and uninfected infants are listed in Table 2.

Pregnancy, delivery and VTR

HCV RNA status was determined in 84 women in pregnancy or at delivery. Viral load was generally not available. These 84 women neither differed in age, HCV risk factor, obstetric outcome or VTR (6.4 versus 6.8%) from the entire cohort nor from those who did not have HCV RNA status determined (VTR 6.4 versus 7.1%). One of 38 (2.6%) HCV RNA negative and 2 of 46 (4.3%) HCV RNA positive women transmitted HCV to their infants. The RNA negative transmitter tested negative in the first trimester. Later testing was not performed. She had tested RNA positive 14 months prior to delivery. The rate of HCV vertical transmission was 3.4 times higher for HIV co-infected women (27% versus 7%, P=0.04). Maternal hepatitis B infection or HCV genotype did not influence transmission risk.

Eighty-nine per cent (280) were delivered vaginally and 11% (6 elective and 28 emergency procedures) by Caesarean section. This compares with Caesarean section rates of 9 to 19% for the hospitals over this time period. There were no infected infants among those delivered surgically. However, in this study, this did not reach statistical significance when compared with those delivered vaginally.

A detailed analysis of the impact of delivery on subsequent infection rate was performed on 154 mothers with detailed obstetric records. This subset was similar to the whole group in age, mode of HCV acquisition and transmission rate. Of this group, 86 infants are of definitive status with six infected. No significant differences were found between infected and uninfected infants in spontaneous rupture of membranes, duration of membrane rupture prior to delivery, blood staining of liquor, surgical or vaginal delivery, or indications of foetal distress. We postulated that the risk of HCV might be increased by perineal tear or episiotomy, but no difference was seen between these groups.

Discussion

There is little data on the magnitude or implications of the evolving hepatitis C epidemic for paediatric services. As most new paediatric infections are acquired vertically,[14] HCV prevalence in childhood is likely to reflect that of women in childbearing years, albeit at a lower rate. In this study, the VTR was 3.5-6.4%. Transmission rates are higher for HIV co-infected women. An association between maternal HCV RNA status and transmission was not demonstrated. HCV RNA status can vary in pregnancy and a single negative test may not reflect viral activity throughout gestation and does not exclude the possibility of HCV transmission.

No association was found between duration of membrane rupture, mode of delivery (perineal tear or episiotomy) and infection rates. The suggestion that Caesarean section prior to membrane rupture might prevent vertical transmission[15] was not proven in this study. However it is notable that all infected infants were delivered vaginally. Large multicentre trials are required to define these potential relationships.

Eleven infants acquired HCV infection. Negative HCV RNA in the first month of life did not exclude infection. However, all infected infants were RNA positive when first tested after one month of age (2-10 months). No infant had a significant blood or bodily fluid exposure after birth. It is likely that negative RNA status at birth reflects recent infection[16] and a level of viraemia below threshold of current testing methods rather than postnatal acquisition. The importance of combining PCR with antibody testing is illustrated by case F. This infant was antibody negative at six months despite being HCV RNA-positive at that time. This probably represents that window during which maternal antibody has been lost and the infant has not yet, or is unable to mount an antibody response. This is supported by waning antibody levels noted in eight of nine infected infants of similar age.

All infants have remained clinically well to date, three have no clinical or biochemical evidence of compromised liver function. The spontaneous loss of detectable viraemia and resolution of transaminases elevation in one patient is encouraging. No corre-

Table 2. Characteristics of infected/uninfected infants

	Infected (n=11)	Not infected (n=162)	
Mother HIV+	3 (27%)	11 (7%)	P=0.04
Mother HBV+	0	7 (4%)	NS
Vaginal delivery	11 (100%)	136 (84%)	NS
Sex:			
Female	6	72	NS
Male	5	90	
Gestation (weeks)			
Median (range)	40 (37-42)	39 (27-43)	NS
Birthweight (kg)			
Median (range)	3.18 (2.88-4.84)	2.9 (1.47-4.33)	NS
Small for gestational age	5 (55%)	53 (33%)	NS
Breast fed	0	5 (3%)	NS
Neonatal abstinence syndrome	8 (73%)	80 (49%)	NS

lation between infant viral load and compromised liver function was seen in any other infected infant. The danger of fulminating hepatitis following superinfection with hepatitis A is largely preventable with early diagnosis and immunisation. Long term follow up is required to define the natural history of HCV infection in children but symptomatic disease in infancy appears rare.

Seventy-seven per cent of uninfected infants had seroreverted by one year of age with no late seroconversions detected to date. Elevated serum transaminases unrelated to intercurrent illness do not necessarily imply HCV infection. Among seroreverting infants, four had a single positive PCR test during the first six months of life. Such results may reflect either laboratory contamination or transient viraemia with subsequent clearance. As PCR testing was carried out with stringent external quality control monitoring the possibility that some infants might experience transient viraemia must be entertained.

Many infants are at risk given the poor social circumstances and chaotic lifestyles of mothers, many of whom fail to attend for antenatal care limiting ability to assess status. Despite this, the complication rate of the antenatal and intrapartum period is low with only 9% requiring emergency Caesarean section. A high percentage of infants were small for gestational age which may be multifactorial. In origin NAS was the primary cause of hospital admission but programmes targeting only infants with NAS for HCV screening would miss significant numbers of infants at risk.

Poor compliance with monitoring schedules of infants might be anticipated in this population, and approximately 22% defaulted completely. Determining appropriate testing schedules and follow up protocols for potentially infected infants is difficult. Delay in clarifying status, coupled with uncertain prognosis and treatment efficacy, contributes to parental confusion and poor clinic attendance. A proactive approach with discussion of HCV and monitoring prior to hospital discharge or early in the neonatal period can decrease the default rate from 30 to 9%.

On the basis of this study, a minimum monitoring schedule for HCV exposed infants is proposed (see Table 3). Umbilical cord blood may be used for HCV antibody testing tested to determine possible perinatal exposure and for baseline liver transaminase evaluation. At six to eight weeks during the normal neonatal check up, HCV PCR and transaminase determination can be repeated. HCV PCR and antibody detection at six months permits early identification of infected infants and allows parental reassurance if both six week and six month PCR tests are negative. Final testing could be scheduled at 18 months both to confirm seroreversion and detect late seroconversions. Such a schedule would facilitate the prompt initiation of immunisation against hepatotropic viruses, and allow more accurate assessment of liver dysfunction in those infected.

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Correspondence to: Dr K Butler, Consultant Paediatrician, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12. Tel.: +353 1 4558111. Email: karina.butler@olhsc.ie

Table 3. Monitoring schedule for infants born to HCV positive women

	Pregnant mother	Birth (cord blood)	Six weeks	Six months	18 months
AST/ALT	√	√		√	
HCV antibody	√	√		√	√
HCV PCR	√		√	√	
HCV viral load	√			√(if PCR +)	
HCV genotype	√			√(if PCR +)	