Viral hepatitis and pregnancy

P. P. Michielsen[1], P. Van Damme[2]

Divisions of [1]Gastroenterology and [2]Community Medicine and Epidemiology, Centre for the Evaluation of Vaccination, WHO Collaborating Centre for Prevention and Control of Viral Hepatitis, University of Antwerp (UIA), B-2610 Antwerpen-Wilrijk.

Abstract

This paper reviews data on the mutual relationship between pregnancy and viral hepatitis and the mother-to-infant transmission of the virus. In the western world, hepatitis A, B or C do not seem to influence the course of pregnancy, or to be associated with foetal risks. In contrast, women who contract a hepatitis E infection in their third trimester of pregnancy have a relatively high probability to develop a fulminant hepatitis. Mother-to-infant transmission of hepatitis A seems to be very uncommon. On the contrary, HBsAg and HBeAg positive mothers have a 80-90% risk to transmit the disease to their offspring, more than 85% of these becoming chronic carriers of HBsAg. The risk depends on the level of viral replication. In HBsAg positive and HBeAg negative mothers the rate of transmission is only 2-15%, these babies rarely become carriers. A possible explanation is the transplacental passage of the HBeAg making the infant tolerant to the hepatitis B virus. As most of the infections occur during or directly after delivery, the neonates are suitable for postexposure prophylaxis. It is recommended by the Centers for Disease Control and Prevention and the American Academy of Pediatrics that newborns of HBsAg positive mothers should receive hepatitis B immunoglobulins within 12 hours after birth concurrently with the first paediatric dose of the vaccine. Vaccination should be completed at 1 and 6 months. This regimen confers a protective efficacy of $\geq$ 90%. Vertical transmission of hepatitis C is considered to be relatively rare, around 11% when HCV-RNA is positive. The highest rates of vertical transmission of HCV are noted in women with high HCV-RNA level or concurrent HIV infection. The risk is extremely low when no HCV-RNA is detected. There is currently no treatment to prevent this vertical transmission ; routine screening of all mothers is unwarranted, and pregnancies among HCV-positive mothers should not be discouraged, but their infants should be tested for anti-HCV at 1 year and followed for the development of hepatitis. Breast feeding does not seem to play an important role in the transmission of hepatitis B and C. (Acta gastroenterol. belg., **1999**, 62, **21-29**).

Key words : hepatitis A, hepatitis B, hepatitis C, vertical transmission, prevention, pregnancy, breast feeding.

Introduction

Viral hepatitis may be caused by a number of well characterized taxonomically different viruses. Conventionally the term is reserved for viral hepatitis caused by hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), Delta (HDV) and hepatitis E virus (HEV).

Hepatitis A is usually a disease of childhood or adolescence in the Third World, where poor hygienic conditions exist. In the western world it is a sporadic infection and usually affects adults. The virus is a picornavirus and is transmitted almost exclusively by the faecal-oral route. Shedding of the virus in stool begins approximately 2 weeks before the onset of clinical symptoms and usually persists for only 1 or 2 weeks after the onset of illness. The entire infection may be anicteric, but occasionally it is associated with severe jaundice. In a very small number fulminant hepatitis occurs. Most patients are completely free of symptoms 1 to 2 months after the onset of their disease. Except for fulminant hepatitis A there are no serious sequelae or chronic forms of the disease.

Hepatitis B is caused by a virus belonging to the hepadnaviridae. The clinical picture of acute hepatitis B is similar to that of hepatitis A. Jaundice occurs in a minority of patients. Five to 10 per cent of patients infected in adult life enter a chronic phase. Persistent active viral replication is characterized by the presence of HBeAg and HBV-DNA by liquid hybridization in serum. This condition can evolve to the HBsAg carrier state, where HBeAg and HBV-DNA (liquid hybridization) are negative and active replication is absent. Some patients infected with precore mutant type HBV can show active replication despite the absence of HBeAg ; HBV-DNA can be detected by liquid hybridization or branched DNA in serum.

HCV is a RNA virus belonging to the flaviviridae. Its genome was first described in 1989. The acute phase is often asymptomatic and usually anicteric. The majority of those infected become chronic carriers and many of them develop slowly progressing chronic active hepatitis and cirrhosis.

HDV is a defective virus which replicates only in the presence of HBV.

HEV is a RNA virus belonging to the caliciviridae. It occurs most frequently in epidemics in Asia, South and Central America. The epidemiology and clinical presentation are similar to that of HAV and it never becomes chronic.

Recently *hepatitis G virus* (HGV) has been identified : it also belongs to the flaviviridae and has a structural similarity with HCV, but few data have been presented that this virus causes acute or chronic liver disease in humans (1).

Although there is considerable overlap in the clinical course of viral hepatitis, the complications may be different. The differences between the viruses may have variable implications in pregnancy on the health of

Correspondence and request of reprints : P.P. Michielsen, M.D., Ph.D., Division of Gastroenterology, University Hospital of Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium.

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mother and infant. The aim of this paper is to review data on the mutual relationship between pregnancy and viral hepatitis and the mother-to-infant transmission of viral hepatitis. Each infection will be discussed separately.

1. Hepatitis A

Acute hepatitis A in pregnancy does not appear to carry a different prognosis than in the nonpregnant patient (2). In developing countries a higher incidence of fulminant disease associated with acute hepatitis A infection during pregnancy has been reported. The reason is uncertain, malnutrition has been suspected (3). There is no evidence that hepatitis A causes birth defects (4). Clinical management of pregnant patients with hepatitis A does not differ from that of those who are not pregnant.

Vertical transmission through the faecal-oral route during delivery or postpartum from an accutely ill mother to the neonate is described (5,6). In those rare circumstances in which the mother has acute hepatitis A infection at the time of delivery, immune serum globulin may be administered to the infant, especially if the mother cares for the baby after delivery. Even under these conditions the risk of transmission to the infant seems very small. Recently, transmission of HAV in utero was described (7).

2. Hepatitis B

2.1. *Mutual relationship of hepatitis B and pregnancy*

Acute hepatitis B infection in pregnant women is no more severe than in non-pregnant women, and is mostly self-limiting (8). Little is known on the effects of pregnancy on the HBV-carrier state. Reactivation (9) and subsidence of viral replication (10) during pregnancy was described.

Early reports suggested that pregnancies complicated by maternal hepatitis, presumed to be type B, were associated with an increased frequency of abortions, congenital malformations and stillbirths. Others could not confirm such relationship. Inadvertent HBV exposure of preembryos with contaminated in vitro fertilization culture medium did not result in any demonstrable damage (11). A retrospective study of 60 pregnant HBsAg carrier women and an equal number of controls without HBV infection showed that pregnancy course and outcome were not affected by hepatitis B antigenaemia (12).

2.2. *Mother-to-infant transmission*

In areas of low endemicity, infection occurs predominantly in adults and largely as a result of sexual contact. In areas of intermediate and high endemicity, infection occurs predominantly in infants as a result of mother-to-infant transmission (vertical transmission) or close contact early in life (horizontal transmission). However, also in the western world maternal-foetal transmission is well recognized and presents a major problem to both obstetrician and paediatrician.

2.2.1. Time of transmission

Indirect evidence suggests that mother-toinfant transmission occurs mainly (> 90%) *during or directly after delivery*. Most infants become HBsAg + between one and 6 months of age, pointing to labour and delivery as the time of transmission of HBV. Mechanisms for the proposed transmission of HBV at or shortly after birth include mixing of maternal and foetal blood during labour, trauma associated with the birth process, minor skin abrasions of the foetus and ingestion of contaminated fluid during labour. It has been shown that HBV can be transmitted by the oral route although the oral dose needs to be 50 times as high as that required for the parenteral route.

In utero transmission of HBV occurs, the extent of which is not exactly known. The rate of transmission across the placenta is estimated 2 to 10% (13). Some authors believe that the infants who cannot be protected by immunoprophylaxis after delivery have an already established infection at birth (14,15). Hepatitis B particles and HBsAg are considered not to pass the placenta. Contamination by transplacental leakage of HBV positive maternal blood induced by uterine contractions during pregnancy in case of threatened abortion or premature labour was suggested to have an important role in the occurrence of intrauterine infections. The contraction of uterine muscles could cause partial breakdown of placental villi in threatened abortion or premature labour and may result in microhaematological leaks across the placenta (16,17).

Even when not infected during the perinatal period, infants of HBV-infected mothers remain at risk of acquiring HBV infection by *horizontal transmission* during the first years of life (18). The breast milk of HBsAg + mothers is often found to be positive for HBsAg, but seems not to play a decisive role in the transmission of HBV (19).

2.2.2. Factors determining perinatal transmission of HBV

The perinatal transmission of HBV is dependent on time of onset of acute hepatitis B during pregnancy, and on the presence of serological markers of high infectivity (HBeAg, HBV-DNA) in the case of chronic infection in the mother.

Women having *acute hepatitis B* in the first or second trimester rarely transmit HBV to their neonates. However, if the mother suffers from acute hepatitis B during the last trimester of pregnancy, the risk of transmission is about 70% (120).

In *chronic hepatitis B*, among mothers who are HBeAg + the risk of transmitting the HBV to their offspring is 80-90%. More than 85% of their infected infants will become chronic HBsAg carriers (21,22). The risk of mother-to-infant transmission is related to the level of HBV-DNA in the sera of the mother.

Infants of HBsAg as well as HBeAg + mothers with HBV-DNA > 5 pg/ml had a significant higher risk of acquiring HBV-carrier state (30/38, 79% at the age of 3 years) than the infants of mothers with low levels of HBV-DNA (0/9) (23). The rate of transmission is about 2-15% when the mother is HBsAg + and HBeAg negative ; in almost all of these infants the HBsAg + state was transient : these babies rarely (10-15%) become carriers through perinatal transmission (22,24). Infection of infants born to HBeAg negative mothers has been associated with fulminant disease (25,26). This outcome has been linked to a HBV variant having a mutation in the precore region of the genome (27).

2.2.3. Pathogenesis of carriership in neonates

Until recently, the frequent evolution to chronicity of hepatitis B infection in neonates was considered to be due to immaturity of the immune system at birth. However, this seems unlikely as neonates have been shown to react very well to hepatitis B vaccination. Thomas *et al.* (28) postulated that HBeAg, which in contrast to HBsAg is able to pass the placenta, may induce tolerance to HBV in neonates through specific suppressor T cells that inhibit the host defence mechanism. As HBeAg in cord serum is only IgG-bound (29), it is suggested that it is transferred from a HBeAg postitive carrier mother to the foetus by a specific trophoblast receptor-mediated mechanism for IgG during the gestational period. Milich *et al.* (30) suggested from experiments in transgenic mice that a helper T cell tolerance specific for HBcAg/HBeAg may be the basic immunologic effect in neonates born to HBeAg positive carrier mothers. Hsu *et al.* (31) showed absence of proliferative response of peripheral blood mononuclear cells to HBcAg in HBeAg positive children with normal aminotransferase levels born to HBV carrier mothers. Also peripheral blood mononuclear cells from neonates born to anti-HBe positive carrier mothers do not proliferate to HBcAg. These children are rarely infected in the perinatal period because of very low or undetectable HBV-DNA. In one infant born to a carrier mother positive for antiHBe who contracted acute hepatitis B showed significant proliferative response to HBcAg. This also explains why infection occurring in infants born to HBsAg + and HBeAg negative mothers usually is transient or fulminant rather than chronic, as no tolerance has been induced in utero (32,33). It was recently shown that immune tolerance to HBV in children is an important factor preventing the emergence of the precore stop codon mutant in children. This mutant is a result of host immune selection in these children (34).

2.2.4. Prevention of mother-to-infant transmission of HBV

Prenatal testing of pregnant women for HBsAg makes it possible to identify in advance those infants at risk for HBV infection. Ideally, the identification of HBsAg carriers should occur late in the third trimester or at the time of delivery. The Centers for Disease Control and Prevention advocate HBsAg determination at the first antenatal care in combination with screening for other routine prenatal tests (35). In HBsAg negative women belonging to a risk group (intravenous drug use, sexually transmittable diseases) and in patients with clinical hepatitis, serology for HBV should be repeated in the third trimester. HBsAg + women identified during screening may have HBV-related liver disease and should be evaluated. Women admitted for delivery who have not had prenatal HBsAg testing should have blood drawn for testing. When the lab tests are pending for more than 12 h after delivery, administration of hepatitis B immunoglobulins (HBIg) to the newborn should be considered.

If HBV infection is diagnosed during pregnancy, invasive prenatal procedures like amniocentesis is not advised and should be avoided too, even though the risk of infection was reported to be small. Prolonged labour should be avoided. At present, caesarean section is not recommended as means of preventing maternal-foetal transmission of HBV. Breast feeding needs not to be discouraged (19).

The finding that HBV is mainly transmitted at birth and not transplacentally makes infants suitable for postexposure prophylaxis at birth.

Passive immunization with HBIg, a preparation containing high concentrations of antibodies to the HBsAg, was among the first methods used to prevent HBV infection. The timing of the initial administration of HBIg is important : HBIg are most effective if given within the first 2 days of life, and the administration of HBIg as soon as possible after birth (preferably within 12 h) has been recommended (14). A Taiwanese study showed that the protective efficacy of a single 1 ml dose of HBIg at birth was 42% rising to 71% in infants receiving 0.5 ml at birth, at 3 and 6 months. HBIg also prolonged the time of onset of infection, beyond 6 months of age (36,37). Delay in administration of passive immunization beyond 48 h significantly decreases the protective effficacy.

Several studies have demonstrated the safety and immunogenicity of both plasma derived and recombinant *vaccines* in newborns (38). Administration schemes of both plasma derived and recombinant vaccines feature 2 or 3 intramuscular injections at monthly intervals, followed by a booster injection 6 to 12 months after the first dose. Premature infants do not have a reduced immune response as compared to term infants (39). An impaired response to HBV vaccine is observed in infants undergoing haemodialysis (40), infants with malignancies (41) and HIV infected infants (42).

Efforts to further reduce the chronic carrier rate and to prevent late infections in infants of HBsAg + mothers focus on the *combination of passive and active immunization* (38). Passively acquired antibody does not interfere with active immunization response to the vaccine. Several observations support the concurrent use of HBIg for the immediate protection and vaccine

for the prolonged protection. With lower dosages of the vaccine, simultaneous use of HBIg is more important than with higher dosages to elicit good protection (protective efficacy $\geq$ 90%). Vaccination courses with higher vaccine dosages give high protective effcacies without concomitant HBIg administration at birth, provided that the first vaccine dose is given at birth and that the second dose follows within 2 months (38). Multiple doses of HBIg have no added advantage over a single dose when followed by hepatitis B vaccination. If vaccination is started at birth, there is no need for a second dose of HBIg. In combined regimens the timing of the first dose of vaccine does not appear to be critical. Late active immunization starting at 3 months of age appears to provide similar protective efficacy as active immunization starting at birth with HBIg at 0 and 3 months of age (36,37,43). The recommendations of the CDC (35) and the American Academy of Paediatrics (34) indicate that a newborn of a HBsAg positive mother should receive 0.5 ml HBIg within the first 12 hours after birth, concurrently with the first paediatric dose of the vaccine. Vaccination should be completed at 1 and 6 months. Protection of HBV infection appears long-lasting, although anti-HBs titres decrease with time. Asymptomatic breakthrough infections seldom occur, even if antibodies are no longer detectable. So far, it appears that there is no need for booster doses, but further follow-up is necessary to confirm such a recommendation. In Belgium, a standard prevention policy does not exist, and the above mentioned recommendations seem to be insufficiently known by paediatricians and gynaecologists (45).

A major clinically relevant factor influencing the protective efficacy rate is the maternal level of HBVDNA (23,46,47 ; Table I).

Failure of passive-active immunization to protect against perinatally transmitted HBV may be due to established infection from in utero transmission (13), high level of maternal HBV-DNA (19,36,37), inadequate active antibody response to the vaccine (4042) or the emergence of S-gene mutations (48-51). Additional preventive measures should be offered to infants from HBeAg positive mothers with high serum levels of HBV-DNA : administration of additional doses of HBIg at birth, to increase the capacity to neutralize HBV (52), or delivery through caesarean section, to reduce the amount of HBV acquired by maternal-foetal transfusion (47). There is uncertainty about the relevance and frequency of S-gene variants associated with vaccine failure. In all series, a significant number of vaccinees (about 15%) develop antiHBc, indicating infection, the amount of clinically relevant infection, indicated by carriers, however, being low (about 2%) (53,54). It is unclear whether the main driving force for selection is active (vaccine-induced) or passive (HBIg) antibody. The most common variants are in the amino-acid 139-147 loop or, less frequently, around the tight loop between amino-acids 121-124 ; these loops are spatially close and constitute the neutralising epitopes of the S-gene (54). The fact that a single amino-acid substitution can lead to a dramatic antigenic change is most important as the pressure on HBV to evolve and select mutants that can replicate in vaccinated individuals increases with widened vaccine coverage (53). The situation has to be carefully monitored. A possible role for third generation vaccines, containing pre-S, in order to avoid escape mutants in the S region, should be further investigated (54).

A summary of the risk factors and prevention of perinatal transmission is presented in Fig. 1.

3. Hepatitis C

3.1. *Mutual relationship of hepatitis C and pregnancy*

The course of hepatitis C infection seems not to be different in pregnant women. There are no reports of foetal or neonatal abnormalities in association with maternal HCV infection. Survival and prematurity rates are comparable regardless of the mother's HCV antibody status (55).

3.2. *Mother-to-infant transmission*

In contrast to HBV, where vertical transmission is an important route, controversial results have been reported on mother-to-infant transmission of HCV.

Table I. — **Maternal level of HBV-DNA and vertical transmission of HBV in hepatitis B carrier mothers in spite of combined active and passive immunization**

Author (ref.)	Immunization schedule	HBV-DNA*	HBV-carrier infants	at age
Lee *et al.* (1988) (37)	HBIg 50 IU combined with vaccination at 1, 5, 9 weeks, 1 year	0 0.3-10 pg/ml 11-80 pg/ml > 80 pg/ml	0/7 6/16 (37.5%) 10/18 (55.5%) 2/2 (100%)	6 months
Ip *et al.* (1989) (19)	HBIg 200 IU combined with vaccination at 0, 1, 2, 6 months	< 5 pg/ml > 5 pg/ml	0/13 9/51 (17.6%)	3 years
del Canho *et al.* (1994) (36)	HBIg 2-300 IU combined with vaccination at 1, 2, 3, 12 months	< 6 pg/mi 7-150 pg/ml > 150 pg/ml	0/24 0/24 7/24 (29%)	1 year

* Liquid hybridisation.

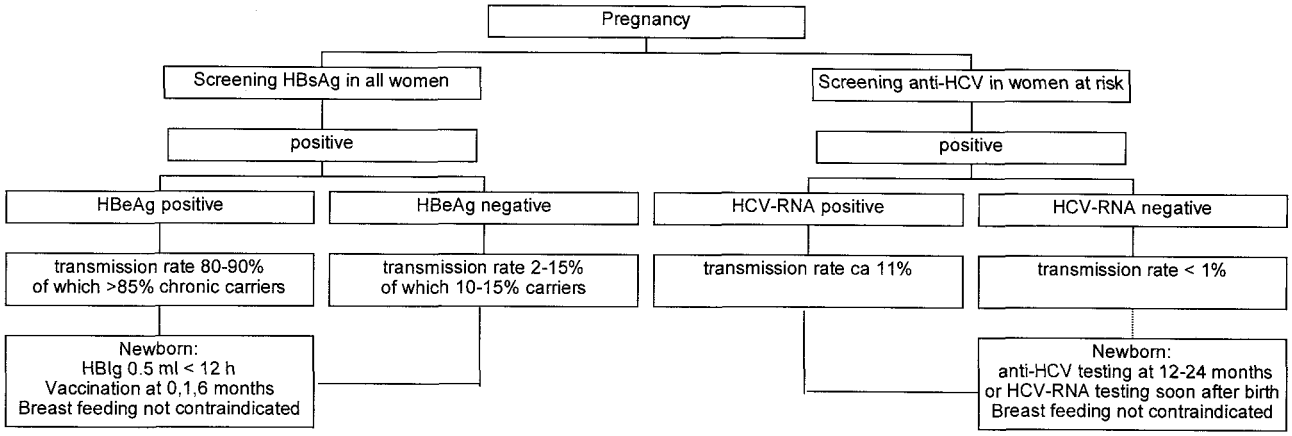

Fig. 1. — Risk factors and recommendations concerning vertical transmission of chronic HBV and HCV in pregnancy.

3.2.1. Does vertical transmission of HCV occur ?

Using sensitive PCR assays, perinatal transmission of HCV has been unequivocally demonstrated by presence of HCV-RNA in some infants born to infected mothers (56-71). Furthermore, several studies revealed almost identical genomic sequences in mothers and their infected infants (61,71-74).

3.2.2. Frequency of vertical transmission of HCV

The reported rates of vertical transmission of HCV vary greatly from 0% (75-81), to 80% (Thaler 1991). An average transmission rate of 6% is supposed (82). Table II summarizes the data on transmission of HCV to newborns from mothers who were anti-HCV positive and HCV-RNA positive from 22 studies (56-70, 75-81) and from mothers shown to be anti-HCV positive but HCV-RNA negative from 17 studies (57, 61-63, 65-70, 75-81) where these data could be retraced. In the former group an average transmission rate of 59/525 (11.2%) is noted, in the latter group of only 2/233 (0.8%). The global transmission rate in the above mentioned studies is 61/758 (8.0%).

Table II. — **Vertical transmission of HCV from anti-HCV positive mothers according to their HCV-RNA status**

Author (year)	Country	Infected children/total number of children born to HCV-RNA + mothers	Infected children/total number of children born to HCV-RNA - mothers	Ref
Thaler *et al.* (1991)	US	8/8		56
Novati *et al.* (1992)	France	3/6*	1/2	57
Reinus *et al.* (1992)	US	0/17	0/6	75
Wejstål *et al.* (1992)	Sweden	3/21		58
Kurauchi *et al.* (1993)	Japan	0/17	0/3	76
Marcellin *et al.* (1993)	France	0/14	0/12	77
Roudot-Thoraval *et al.* (1993)	France	0/8	0/9	78
Lin *et al.* (1994)	Taiwan	1/15		59
Ni *et al.* (1994)	Taiwan	2/11		60
Ohto *et al.* (1994)	Japan	3/32	0/22	61
Giacchino *et al.* (1995)	Italy	2/19	0/12	62
Manzini *et al.* (1995)	Italy	0/27	0/8	79
Matsubara *et al.* (1995)	Japan	3/21	0/10	63
Moriya *et al.* (1995)	Japan	2/87		64
Paccagnini *et al.* (1995)	Italy	9/23	1/14	65
Resti *et al.* (1995)	Italy	5/12	0/10	66
Zanetti *et al.* (1995)	Italy	8/64	0/52	67
Zuccotti *et al.* (1995)	Italy	6/21	0/16	68
Benali *et al.* (1996)	France	1/34	0/16	69
Fischleretal. (1996)	Sweden	0/40	0/14	80
Pipan *et al.* (1996)	Italy	0/18	0/7	81
Sabatino *et al.* (1996)	Italy	3/10	0/20	70
Total		59/525 (11.2%)	2/233 (0.8%)	

* including 1 mother considered indeterminate because of discordant result of 2 assays.

3.2.3. Factors influencing the transmission rate

- The risk of vertical transmission seems to be related to the *maternal viremia* levels. It was reported that all mothers who transmitted HCV to their infants had HCV-RNA titers of at least 10^6 genome equivalents per ml as determined by quantitative PCR (61) or 5×10^6 genome equivalents per ml by branched DNA assay (64). Lin *et al.* (59) reported vertical transmission in only 1 neonate of a mother with an extremely high titer of HCV-RNA (10^{10} copies/ml with competitive PCR) and not in the remaining 14 neonates born to mothers with moderate amounts of HCV-RNA (10^5-10^6 copies/ml). However, no vertical transmission of HCV was observed by Pipan *et al.* (81), not even in mothers with HCV-RNA above 10^6 genome equivalents per ml as detected by branched DNA. Mothers being anti-HCV positive but HCV-RNA negative only very rarely seem to transmit HCV (Table II). Most reports give no transmission, only Novati (57) and Paccagnini (65) reported 1 transmission each.

- *HIV coinfection* seems to result in higher rates of perinatal infection, ranging from 0 to 36% (56,57,65,67, 74,80) with an average of 16% (82). It is supposed that HIV-induced immunosuppression results in higher viremia levels as was demonstrated by Zanetti *et al.* (67).

- The influence of *genotypes* of HCV in vertical transmission is unclear. Zucotti *et al.* (68) detected HCV infection in 6/13 infants born to women infected with HCV genotypes 1b or 3a but none of 8 whose mothers have 1a or 2b infection. Other authors (61,64, 67,74) reported no evidence of selective transmission of particular HCV genotypes.

3.2.4. Time of transmission

As cord blood samples mostly are found HCV-RNA negative in infected infants, becoming positive after 1 week to 3 months (63,65,70), transmission of HCV is most probably caused by exposure to the mother's blood during delivery. There are insufficient data on the influence of the mode of delivery on the rate of HCV transmission : Chang *et al.* (83) reported a significantly higher rate of HCV transmission in infants delivered vaginally compared with caesarean section, this was not the case in the report of Fischler *et al.* (80).

3.2.5. Influence of breast feeding

HCV-RNA was detected in colostrum of HCV infected mothers, although in much lower titers as in serum (84). However, there is no evidence of transmission of HCV by breast feeding (79,80,84).

3.2.6. Prevention of vertical HCV transmission

Although administration of immune serum globulin has been recommended to prevent perinatal transmission of non-A, non-B hepatitis (85), there are no studies of the efficacy and safety of immune serum globulin for prevention of perinatal transmission of HCV (86,87).

3.2.7. Course of the disease in infants

In almost all newborns infected with HCV from their mother the disease runs a symptom-free course and is detected by screening. As in adults, approximately 80% of the children become chronically infected. A review of current data is given by Bernard (88). Passively acquired HCV antibodies are lost within 18 months of life and their persistence means HCV infection (65).

3.2.8. Recommendations

Pregnancy is not considered contraindicated in HCV-infected individuals (89). Since the perinatal transmission rate of HCV is low and there are no measures to prevent perinatal infection, universal screening is not considered cost-effective. In risk groups (intravenous drug users, prostitutes, women with HIV infection, patients who received blood transfusions before the routine HCV testing, women whose partners are seropositive, women with other sexually transmittable diseases, women with multiple sexual partners) HCV screening is advisable. When HCV infection is documented, HCV-RNA determination is useful. When HCV-RNA is repeatedly negative, HCV vertical transmission is almost excluded. When HCV-RNA is positive, perinatal counseling regarding the neonatal risk of HCV infection should be offered. Currently, data are lacking to support any change in routine perinatal or labor practices in patients with HCV. There is no evidence that breast feeding transmits HCV from mother to baby ; therefore it is considered safe (89). Babies born to HCV-positive women should be tested for anti-HCV at 1 year (89) or 18-24 months (90). Other authors recommend HCV-RNA screening soon after birth and in case of negativity, repeating the assay at 6 and 12 months of age (82).

A summary of the risk factors and the recommendations concerning HCV in pregnancy is presented in Fig. 1.

4. Delta hepatitis

HDV is rare in pregnant women and is uncommonly transmitted to infants (91).

5. Hepatitis E

A high probability to develop fulminant hepatitis E infection has been reported among women who contract a hepatitis E infection in their third trimester of pregnancy (92,93). A case fatality rate of more than 20% has been described. Spontaneous abortion and intrauterine death appear to be common in pregnant women infected with hepatitis E. There has been reported a higher rate (12.4%) of abortion and intrauterine death among women with nonfulminant and uncomplicated hepatitis E infection (93). Recently, two cases of severe hepatitis E in pregnancy in patients

returning to the UK from the Indian subcontinent were reported (94).

Little is known about vertical transmission of hepatitis E from infected mothers to their infants. Recently, 8 babies born to mothers infected with HEV in the third trimester were studied (95). The authors concluded that 6/8 infants born from mothers with HEV in the third trimester had clinical, serological or virological evidence of HEV infection : 5 had HEV-RNA in cord or birth blood (2 died within 24 h having elevated ALT, 1 was icteric with raised ALT, 2 had elevated ALT suggesting anicteric hepatitis) ; in 1 infant with normal liver tests and absence of HEV-RNA at birth ; the HEV antibodies persisted at 6 months of age. In the remaining 2 infants with normal liver tests and no detectable HEV-RNA at birth, HEV antibodies disappeared before 6 months of age, suggesting passive transmission of IgG antibodies. It can be concluded from these data that HEV is commonly transmitted from infected mothers to their babies, that there is intrauterine transmission and that this transmission causes significant perinatal morbidity and mortality. It may be speculated that intrauterine HEV infection may lead to abortion and intrauterine death, common in pregnant women with HEV.

6. Hepatitis G

Preliminary data indicate that the risk of vertical transmission seems to be high (30-60%) (96-99), associated with high maternal viremia (99) and independent of the transmission of HCV (98). The clinical significance of HGV, however, remains to be established (1).

7. Other viruses

Other viruses may also cause medical consequences during pregnancy. Cytomegalovirus may cause hepatitis during pregnancy, even of the fulminant type and often with congenital infection of the newborn (100). Measles during pregnancy may cause maternal hepatitis and adverse outcomes for the infant : i.e. prematurity, spontaneous abortion and death (101).

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