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Research Article

Natural History of Vertically Transmitted Hepatitis C Virus

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Abstract

Background: Hepatitis C Virus **(HCV)** is an endemic disease with chronic sequelae that include cirrhosis and liver cancer. Children acquire the disease mainly via the maternal-infant route. This study investigated its prevalence in pregnant women and the natural history of its vertical transmission.

Methods: This prospective study involved 618 randomly selected pregnant women in Al-Ain City (Abu Dhabi, UAE). Participants were screened in the first trimester by second-generation Enzyme-Linked Immunosorbent Assays **(ELISA-2).** Positive samples were further tested by third-generation ELISA (ELISA-3), third-generation recombinant immunoblot assay for detection of antibodies (anti-HCV), and Reverse Transcriptase-Polymerase Chain Reaction **(RT-PCR)** to detect HCV-RNA. Infants of mothers with positive anti-HCV antibody or HCV-RNA were followed for several years.

Results: Twenty-five women (4.0%) had positive ELISA-2; of which eleven (1.8%) had positive ELISA-3, nine (1.5%) had positive anti-HCV antibody, and three (0.5%) had positive HCV-RNA. All nine infants of mothers with positive anti-HCV antibody had positive anti-HCV antibody at 1, 6, and 12 months of age. All three infants of mothers with positive HCV-RNA had positive HCV-RNA and elevated Alanine Transaminase (ALT) for several years. All six infants of mothers with negative HCV-RNA had negative HCV-RNA and normal ALT at 1, 6, and 12 months of age.

Conclusion: The prevalence of positive anti-HCV antibody in infants of mothers with positive anti-HCV antibody was 9/9 at 12 months. The prevalence of HCV infection (positive HCV-RNA) among mothers in our region is about 0.5%. The prevalence of positive HCV-RNA in infants of mothers with positive HCV-RNA was 3/3 and of mothers with negative HCV-RNA 0/6 (p=0.012). These results justify long-term monitoring of infants born to mothers with positive anti-HCV or HCV-RNA.

Introduction

Hepatitis C virus **(HCV)** is a major cause of acute and chronic hepatitis worldwide. The World Health Organization estimated 170 million individuals are infected with HCV. Its prevalence, however, varies among different countries, with a large number of reported cases from Egypt due to the use of contaminated parenteral anti-schistosomal therapy [1-2].

Abou t 3% of the world's population is infected with HCV, with the highest prevalence occurring between 30 and 49 years of age [1] In the United Arab Emirates **(UAE),** the prevalence of HCV among blood donors of 26 to 45 years of age is 1.7% and of those less than 25 years of age is 0% [3].

Sixty percent of patients with acute HCV infection become chronic carriers, predisposing them to serious liver diseases. Cirrhosis occurs in about 20% of infected patients. Up to 20% of patients with cirrhosis develop liver cancer [4]. With the current blood screening programs that ceased transfusion-associated HCV infection, children acquire the disease mainly via the maternal-infant route [5].

Mother-to-infant HCV transmission is well documented [4]. Nevertheless, limited data are available in highly diverse cultures, such as the UAE. This report describes: (1) the prevalence of HCV among pregnant women and (2) the outcome of its vertical transmission in Al-Ain Medical District (Abu Dhabi, UAE).

Methods

The study participants had attended prenatal care in Al-Ain Medical Districts between June 2001 and June 2002. Seven hundred randomly selected mothers (representing about 10% of total deliveries) were approached. Six hundred eighteen (88%) mothers consented to the study; 104 (16.8%) mothers were UAE citizens and 514 (83.2%) were UAE residents (expatriates) from the Middle East, Indian sub-continent and Africa. Maternal data included transfusion history, parity, mode of delivery and breast feeding. HIV antibody and hepatitis B surface antigen were performed for routine antenatal care and were negative in all participants. Inclusion criteria were all pregnant

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Table 1: Family 1: Serology profiles of HCV-infected infant and her mother.

	Infant			Mother		
Age	ALT	Anti-HCV	HCV-RNA	ALT	Anti-HCV	HCV-RNA
1st trimester				70	+	+++
1 mo	38	+	+	nd	nd	++
3 mo	40	+	nd	38	nd	nd
8 mo	44	nd	+ +	64	nd	+
13 mo	90	nd	+	na	nd	nd
27 mo	52	+	+/-	94	+	nd
42 mo	192	nd	++	40	+	++
59 mo	36	+	+/-	110	nd	nd

ALT, alanine transaminase (in IU/L; normal <40); HCV-RNA (copies/mL): +/- = <2 x10^5; + = 2 x10^5 to 1 x10^6; ++ = 1 x10^6 to 5 x10^6; +++ = >5 x10^6. "nd", not done.

women who consented to the study. Exclusion criteria were women who refused to participate in the study.

Consented mothers were screened in their first trimester by second-generation ELISA (ELISA-2, UBI HCV EIA 4.0, done in duplicates in the Department of Microbiology, College of Medicine and Health Sciences - UAE University). Positive serology was confirmed by third-generation ELISA (ELISA-3, BioElisa HCV of Biokit, S.A. Barcelona HCV - Bio Barcelona, Spain). Mothers with positive ELISA-3 had anti-HCV antibody immmunoblot assay (anti-HCV, Bioblot HCV - Bio Kit Barcelona, Spain) and RT-PCR for HCV-RNA. A positive HCV-RNA indicated the presence of 272 and 256 base pair band PCR products. All procedures and interpretations were performed according to the manufactures' instructions.

Infants born to mothers with positive anti-HCV antibody were investigated by anti-HCV assay, HCV-RNA PCR and serum ALT (upper limit normal, 40 IU/L) >12 months of age. Mothers and infants were considered HCV-infected if HCV-RNA was positive.

The study was approved by the Committee for Protection of Human Subjects of the University of Texas Health Science Center at Houston and Al-Ain Medical District Human Research Ethics Committee and Federal Ministry of Health. A written informed consent was obtained for each participant. The data were analyzed using SPSS (v11.5).

Results

Six hundred eighteen mothers were screened by ELISA-2; 25 (4.0%) women were tested positive and underwent further investigation. Eleven (1.8%) women had positive ELISA-3, nine (1.5%) had positive anti-HCV, and three (0.5%) had positive HCV-RNA. Mothers with positive HCV-RNA were considered infected.

Infants of mothers with positive anti-HCV were monitored until at least 12 months of age. All infants had anti-HCV testing at one month of age. The three infants of mothers with positive HCV-RNA all had positive HCV-RNA, positive anti-HCV antibody, and elevated ALT for at least 12 months of age. These infants, considered HCV-infected, were singleton births with term deliveries. One of the infants was delivered by C-section for transverse position.

Table 2: Family 2: Recent profiles of HCV-infected mother and her two sons.

	Age (yr)	ALT (IU/L)	Anti-HCV	HCV-RNA*	Liver Fibroscan
Mother	46	39	nd	1,234,006	Stage 3 liver fibrosis (10.1 kP)
Son	15	38	nd	404,464 genotype indeterminate	Stage 1-2 liver fibrosis (7.2 kP)
Son	10	41	reactive	nd	Nd

* Values are viral load.
kP, kilo Pascal; "nd", not done.

Table 3: Family 3: Recent profiles of HCV-infected parents and their 4 children.

	Age (yr)	Anti-HCV	HCV-RNA*	Liver Fibroscan
Mother	41	reactive	42,970	Stage 0 liver fibrosis (3.9 kP)
Father	53	reactive	1,078,785, genotype 4	nd
Daughter	16	nd	nd	nd
Daughter	14	nd	nd	nd
Daughter	11	nd	nd	nd
Daughter	9	non-reactive at 1 yr of age	nd	nd

* Values are viral load.
kP, kilo Pascal; "nd", not done.

The representative profile for infant #1 is shown in (Table 1). This infant girl had positive HCV-RNA at 1, 8, 13, 27, 42, and 59 months of age. Her anti-HCV antibody was also consistently positive up to 59 months. She also had elevated ALT. Nevertheless, she developed normally. Recent profiles for the other two infants are shown in Tables 2,3.

The six infants of mothers with negative HCV-RNA all had negative HCV-RNA, negative anti-HCV antibody and normal ALT at 12 months of age. Thus, the vertical transmission in HCV-RNA negative mothers was 0/6 and in HCV-RNA positive mothers was 3/3 (p=0.012; Fisher's exact test).

Discussion

In this study cohort, nine (1.5%) mothers had anti-HCV antibody and three (0.5%) had HCV-RNA. The three infants of mothers with HCV-RNA had positive HCV-RNA for >12 months. The six infants of mothers without HCV-RNA had negative HCV-RNA at 12 months. Thus, infants of mothers with HCV-RNA need treatment and long-term monitoring. The results also advocate for screening high-risk pregnant women for HCV-RNA, since the impact of this disease on the children is substantial.

As shown in Table 1, the mother of Family #1 had high HCV-RNA titer in the first trimester. Her infant also had a high viral titer and markedly elevated ALT at 42 months of age. For Family #2, high viral titer was present at 15 years of age along with evidence of liver disease (Table 2). Therefore, long-term monitoring and anti-viral treatment of these patients are warranted.

For Family #3, both parents had high viral titers (Table 3); one parent had a history of blood transfusion and one had unknown risk factors. Reported risk factors for mother-to-infant transmission include high viral load, co-infection (e.g., HIV and HBV), mode-of-delivery, and type of infant feeding [6,7].

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Recent epidemiology of HCV and HBV in the UAE is summarized in (Tables 4-5). The frequency of both infections increases with age, which reflects accumulative risks of the viral exposure (Table 4). Consistently, the prevalence of HCV in our premarital screening program (Table 5) is similar to that found in our study (about 0.5%).

Table 4: HCV and HBV cases notified in Abu Dhabi (2010-2012).

		Age (y)						
Year		<1	1 to <5	5 to <15	15 to <25	25 to <35	35 to <45	≥45
2010	**HCV**	1		2	12	26	25	56
	HBV	2	2	3	22	30	28	57
2011	**HCV**	1	2	3	13	24	26	69
	HBV	2		7	20	30	27	57
2012	**HCV**	0	1	1	7	17	21	49
	HBV	1	1	1	17	25	21	48

Table 5: Seroprevalences of HCV and HBV in the premarital screening program (2011-2012).

Year	Results	HCV	HBV
2011 (n=9,475)	Reactive	43 (0.5%)	100 (1.0%)
	Equivocal	2 (0.2%)	2 (0.2%)
	Non-reactive	9,419 (99.5%)	9,362 (99%)
2012 (n=7,734)	Reactive	34 (0.4%)	60 (0.8%)
	Equivocal	2 (0.2%)	2 (0.03%)
	Non-reactive	7,695 (99.5%)	7,672 (99.2%)

Vertical transmission is the most common route of infection in children. Several studies have reported a rate of mother-to-infant HCV transmission of about 10% [8-10]. HCV infection in children has a different course than that in adults; children have higher rate of spontaneous clearance. High maternal HCV load and HIV co-infection have been shown to increase the risk of infection in the offspring [8]. In our study, the three mothers of HCV-RNA were HIV negative. Two of the three infected infants were born by natural delivery. One infant (Table 1) was delivered by C-section. All infected infants were breast-fed.

Effective monitoring hinges on availability of sensitive screening tests. Third-generation ELISA is highly sensitive (97%) and specific (99%) for detecting HCV. Detection of anti-HCV antibody in the blood reflects a prior exposure to the virus, but not necessarily active infection. To verify active infection, children with positive ELIZA-3 or positive anti-HCV antibody should undergo HCV-RNA testing. Qualitative HCV-RNA testing is adequate; persistent positive HCV-RNA for at least 6 months indicate a chronic infection. Quantitive HCV-RNA is usually used to follow treatment responses and to measure treatment efficiency in certain genotypes [8]. As shown here, molecular detection of HCV-RNA is required, since only infants of mothers with positive HCV-RNA need treatment and long-term follow-up. Since effective anti-viral treatments are readily available, the need for screening infants by HCV-RNA is critical [11]. It is unknown whether delivering infants via C-section and avoiding breastfeeding would reduce transmission risk (as is the case in HIV).

In conclusion, this study shows the prevalence of HCV-RNA among pregnant women is about 0.5%. The frequency of mother-to-infant vertically transmission is 100%. The infection in infants is chronic and causes long-term sequelae. Treatment of HCV is available and effective. Therefore, screening mothers and infants for HCV-RNA is advisable, especially in high risk populations (e.g., people who received contaminated parenteral anti-schistosomal therapy) [12-14].

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