Hepatitis C Vertical Transmission (Laboratory Testing in Mothers and Neonates)

Original Article

Ahmed Mostafa Abdelaziz[1] and Alaa Kandil[2]

[1]Department of Obstetrics and Gynecology, [2]Department of Hepatology, Gastroenterology and Infectious Diseases, Faculty of Medicine, Benha university, Egypt

ABSTRACT

Background: Infection with the hepatitis C virus (HCV) affects 2%-3% of the world's population. Egypt has the highest recorded prevalence of HCV in the world, reaching 14.7% for HCV-antibody (Ab) positivity among 15- to 59-year-olds in 2008. The natural history of vertically acquired HCV in children is uncertain, with the majority (73–92%) suffer continual infectious state but stay asymptomatic in the first few years.

Aim: To investigate the diagnostic performance and characteristics of maternal HCV RNA testing in predictability of developing neonatal positive HCV Ab and positive HCV RNA.

Methodology: At Benha University hospital from 2016 to 2018 Obstetrics and Gynecology department in collaboration with Hepatology, Gastroenterology and infectious disease department, HCV RNA +ve pregnant women were recruited into a cohort study from gestation to 6 months after delivery. Maternal and child research data were collected via HCV antibody testing and HCV RNA testing.

Results: Maternal HCV RNA had statistically significant low diagnostic performance and characteristics in prediction of developing neonatal positive HCV Ab (AUC = 0.749, SE = 0.050, Pvalue $<$ 0.001, 95% CI = 0.651 – 0.847 , cutoff $\geq$ 4.7, sensitivity = 0.839, specificity = 0.614) and positive HCV RNA (AUC = 0.787, SE = 0.080, P value = 0.007, 95% CI = 0.629 – 0.944, cutoff $\geq$ 9.2 sensitivity = 0.625, specificity = 0.870).

Conclusions: Possibly, there is inadequate or incomplete HCV screening of vulnerable neonates due to, low maternal health-care compliance. Complete testing of all neonates at risk of vertically acquired HCV requires to be noted in medical recording system as early management intervention could influence disease course.

Key Words: Infectious disease vertical transmission; offspring; hepatitis C.

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Corresponding Author: Ahmed Mostafa Abdelaziz, Department of Obstetrics and Gynecology, Faculty of Medicine, Egypt, **E-mail:** ahmedabdelaziz122333444@gmail.com

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INTRODUCTION

Even though having the highest hepatitis C virus infection prevalence globally , the ongoing level of HCV incidence in Egypt and its drivers are poorly understood. Whereas HCV mother-to-child infection is a well-established transmission route, there are no estimates of HCV infections resulting from vertical transmission for any country, including Egypt.[1]

In Egypt, vertical mode of HCV transmission is not known but it is estimated To be steadily increasing, due increasing number of females of childbearing age living with chronic HCV. guidelines regarding lab screening for at-risk children differ . Some recommend HCV RNA testing at or soon after 2 months of age and HCV antibody (anti-HCV) testing after 18 months of age. Others recommend only anti-HCV testing after 18 months of age. Although risk of transmission is rare in HCV RNA negative gestations , there is still some risk associated with low-level viraemia not being detected.[2]

Factors leading to low compliance for performance of HCV testing involve inconvinence in the health system for risky gestations and under diagnosis of mothers with HCV infection; couples opinion that low risk of vertical transmission exists, fear of HCV infection stigma, lifestyleaffection.[3-5]

The natural history of vertically acquired HCV in children is uncertain, with the majority (73–92%) suffer continual infectious state but stay asymptomatic in the first few years. Liver biopsies characteristically reveal hepatic inflammation and fibrosis and although rare (<2%), progression to decompensated hepatic cirrhosis may occur in childhood. Management of adult HCV infection with direct-acting antiviral agents leads to high rates of cure with few side effects; however, pegylated interferon in combination with ribavirin remains typical management protocol for children with chronic HCV. Trials of direct antiviral agents (DAAS) in children are in progress, thus timely clinical diagnosis is a significant issue.[6-10]

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Infection with the hepatitis C virus (HCV) affects 2%-3% of the world's population. Egypt has the highest recorded prevalence of HCV in the world, reaching 14.7% for HCV-antibody (Ab) positivity among 15- to 59-year-olds in 2008. The viremic population of Egypt was estimated at over 6 million in 2008. This epidemic has been linked, in part, to a mass campaign of parenteral antischistosomal therapy in the 1950s-1980s, during which millions of people received intravenous treatment in rural community campaigns.[11]

The current pattern of HCV prevalence is higher in rural areas, increases with age, and is higher in men compared to women. Universal screening of blood and blood products was introduced in Egypt in June 1993.8 However, nosocomial and other health care-related exposures remain associated with HCV among adults and children.[12]

Parental, and especially the mother's, HCV serostatus, is an additional risk factor for prevalent HCV infection among children. Globally, vertical transmission appears to be the most important route of HCV transmission among children. However, the contribution of vertical transmission to HCV incidence and its public health consequences remain unknown. Maternal human immunodeficiency virus (HIV) coinfection doubles the odds of HCV vertical transmission, but the mother's age, parity, HCV genotype, or breastfeeding do not appear to be associated with the risk of vertical infection.[13,14]

There are no nationally representative estimates of HCV prevalence among children under 15 years of age in Egypt. However, a systematic review of HCV in Egypt identified six studies assessing HCV prevalence among school children between 1992 and 2005 and found a range of HCV-Ab-positive prevalence from 2.1% to 12.1%.13 In a cohort followed from birth to 5 years of age in Lower Egypt, the estimated HCV incidence was significantly higher during the first year of life, compared to the 1- to 5-year age group (3.8 and 2.0 per 1,000 person-years, respectively). With over 80 million inhabitants, Egypt is the most populous Arab country and continues to experience high annual population growth (1.5%-1.9% in 2010- 2015).28 Despite a large reservoir of HCV infection in the adult population as well as a relatively high fertility rate, no published studies estimating the extent of vertical transmission in Egypt were identified.[15,16]

Though HCV prevalence among adults in Egypt is well characterized, the level of ongoing HCV incidence and relative contribution of various transmission routes remain uncertain and a subject of discussion.[17,18,19]

AIM

To investigate the diagnostic performance and characteristics of maternal HCV RNA (x10^6 copies/mL) testing in predictability of developing neonatal positive HCV Ab and positive HCV RNA

METHODOLOGY

The current research study was conducted from from 2016 to 2018 at Benha University Hospital (obstetrics and gynecology department in collaboration with Hepatology,Gastroenterology and infectious diseases department) in which 100 cases HCV RNA +ve pregnant women were recruited into a cohort study from gestation to 6 months after delivery. Maternal and child research data were collected as regards age ,BMI,maternal exposure (e.g dental interventions),neonatal exposure (e.g ROM>6hrs) HCV antibody testing and HCV RNA testing results .

Statistical methods

The collected research data were coded, tabulated, and statistically analyzed by usage of IBM SPSS statistics (Statistical Package for Social Sciences) software version 18.0, IBM Corp., Chicago, USA, 2009. Descriptive statistics were performed for quantitative research data as minimum& maximum of the range in addition to mean±SD (standard deviation), while it was done for qualitative research data as number and percentage. Inferential statistical analyses was conducted for quantitative variables by usage , ANOVA test with post hoc Tukey test for more than two independent groups. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions and Fisher's Exact test for variables with small expected numbers with post hoc Bonferroni test. Logistic regression was used to find out independent factors affecting neonatal HCV findings. ROC curve was used to evaluate the performance of different tests differentiate between certain groups. The level of significance was taken at *P value* < 0.050 is statistically significant, otherwise is non-significant. Diagnostic characteristics were calculated as follows: Sensitivity = (True positive test / Total positive golden) x 100.Specificity = (True negative test / Total negative golden) x 100

RESULTS

(Table 1) and (Figure 1) show that: More than half of neonates had positive Ab (n=56 cases,56 %), and less than tenth of cases had positive RNA.(8%)

The above figure reveals that from 100 neonates 44 cases were Ab negative and 56 cases were Ab positive from those 48 cases were RNA negative and 8 cases were positive.

(Table 2) and (Figures 2,3) show that: Maternal RNA was highest in Ab +ve/ RNA +ve,(11.0±5.3x10^6 copies/ mL) followed by Ab +ve/ RNA –ve(7.3±3.5 x10^6

copies/mL) and least in Ab –ve (4.6±2.7 x10^6 copies/mL)with statistical significant difference between them(p value<0.001) . ROM >6 hours was highest in Ab +ve/ RNA +ve(10/48,20.8%), followed by Ab +ve/ RNA –ve (3/8, 37.5%)and least in Ab –ve(3/44, 6.8%) with statistical significant difference between Ab +ve/ RNA +ve and Ab –ve research categories(p value =0.042). Cesarean delivery was lowest in Ab +ve/ RNA +ve(3/8,37.5%), followed by Ab +ve/ RNA –ve(22/48,45.8%) and highest in Ab –ve(24,54.5%) with no statistical significant difference. (*p value* =0.594)

(Table 3) shows that: Maternal viral load and ROM >6 hours were statistically significant factors that increase the risk of developing neonatal positive HCV Ab (*p value* <0.001, 0.042, consecutively) and positive HCV RNA(p value=0.001, 0.029,consecutively)

(Table 4) shows that: Maternal HCV RNA had statistically significant low diagnostic performance and characteristics in prediction of developing neonatal positive HCV Ab(AUC = 0.749, SE = 0.050, *Pvalue*<0.001, 95% CI = 0.651–0.847, cutoff ≥ 4.7, sensitivity = 0.839, specificity = 0.614) and positive HCV RNA (AUC = 0.787, SE=0.080, *P value* =0.007, 95% CI = 0.629–0.944, cutoff ≥ 9.2 sensitivity = 0.625, specificity = 0.870).

Table 1: Characteristics of the studied cases

Characteristics		Mean±SD	Range
Maternal Age (years)		31.6±2.6	25.0–38.0
Maternal BMI		24.2±1.6	19.0–27.3
Parity		2±1.0	0.0–4.0
Maternal RNA (x10^6 copies/mL)		6.4±3.8	0.5–18.3
Neonatal gestational age (weeks)		39.1±1.0	37.0–41.0
		N	%
Maternal exposures	Dental interventions	23	23.0
	Operations	23	23.0
	Transfusions	16	16.0
	IV abuse	0	0.0
Neonatal exposures	Amniocentesis	0	0.0
	Scalp electrodes	0	0.0
	ROM >6 hours	16	16.0
	Cesarean delivery	49	49.0
Neonatal HCV Ab testing	HCV Ab +ve	56	56.0
	HCV RNA+ve	8	8.0
Neonatal HCV category	Ab -ve	44	44.0
	Ab +ve/ RNA -ve	48	48.0
	Ab +ve/ RNA +ve	8	8.0

Total=100

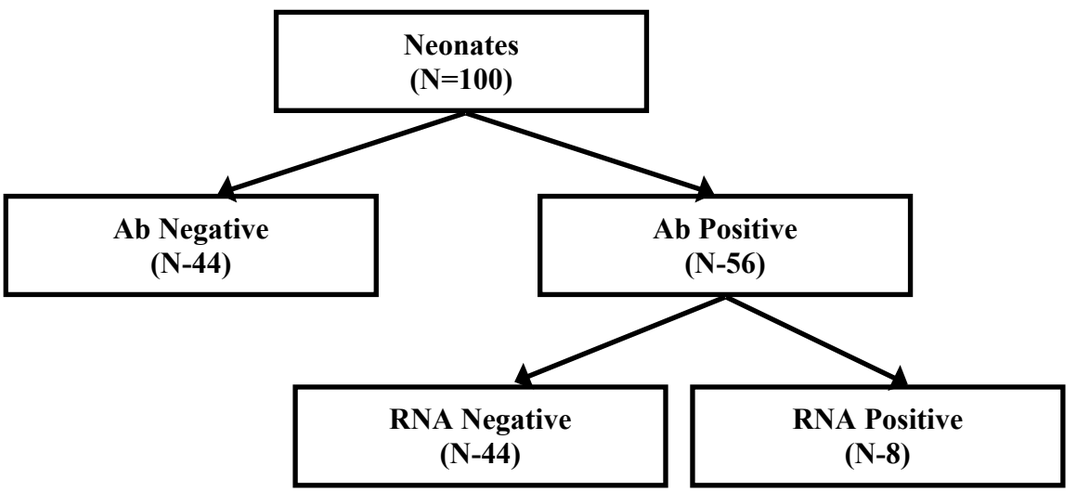

Fig. 1: HCV status among neonates

Table 2: Comparison between HCV laboratory testing categories

Characteristics		Ab –ve (N=44)	Ab +ve/ RNA -ve (N=48)	Ab +ve/ RNA +ve (N=8)	*P*
Maternal Age (years)		31.4±2.7	31.7±2.5	32.5±2.9	^0.573
Maternal BMI		24.1±1.7	24.3±1.4	23.9±1.9	^0.837
Parity		1.0±1.0	2.0±1.0	1.0±1.0	^0.615
Maternal RNA (x10^6 copies/mL)		4.6±2.7a	7.3±3.5b	11.0±5.3c	^<0.001*
Neonatal gestational age (weeks)		39.0±1.0	39.0±1.0	39.6±1.5	^0.323
Maternal exposures	Dental interventions	10 (22.7%)	11 (22.9%)	2 (25.0%)	#0.990
	Operations	9 (20.5%)	12 (25.0%)	2 (25.0%)	#0.866
	Transfusions	8 (18.2%)	7 (14.6%)	1 (12.5%)	#0.861
Neonaotal exposures	ROM >6 hours	3 (6.8%)a	10 (20.8%)ab	3 (37.5%)b	#0.042*
	Cesarean delivery	24 (54.5%)	22 (45.8%)	3 (37.5%)	&0.594

^ANOVA test with post hoc Tukey test, #Chi square test with post hoc Bonferroni test, &Fisher's Exact test, Homogenous groups had the same letter (a,b,c), *Significant

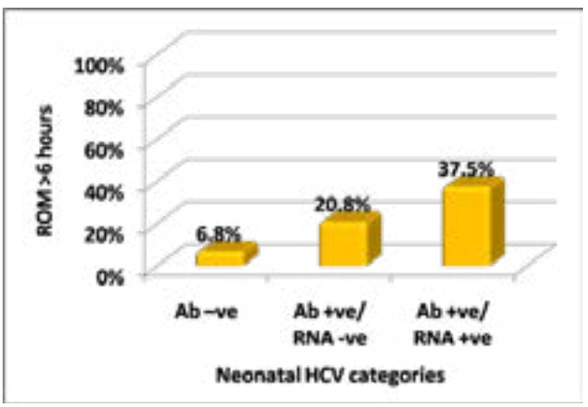

Fig. 2: Comparison between Neonatal HCV categories regarding ROM >6 hours

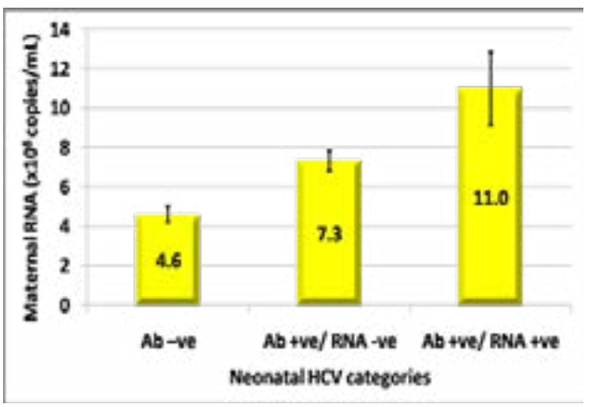

Fig. 3: Comparison between Neonatal HCV categories regarding maternal viral load

Table 3: Logistic regression for factors affecting developing neonatal positive HCV Ab and positive HCV RNA

Variables	β	SE	*P*	OR (95% CI)
		Positive HCV Ab		
Maternal RNA (x10^6 copies/mL)	0.356	0.093	<0.001*	1.428 (1.190–1.713)
ROM >6 hours	1.451	0.715	0.042*	4.266 (1.050–17.327)
Cesarean delivery	-0.575	0.480	0.231	0.563 (0.220–1.442)
Constant	-1.827	0.599	0.002*	
		Positive HCV RNA		
Maternal RNA (x10^6 copies/mL)	0.368	0.115	0.001*	1.445 (1.153–1.810)
ROM >6 hours	2.332	1.071	0.029*	10.303 (1.262–84.139)
Cesarean delivery	-0.725	0.894	0.417	0.484 (0.084–2.795)
Constant	-5.917	1.503	<0.001*	

β: Regression coefficient, SE: Standard error, OR: Odds ratio, CI: Confidence interval, *significant

Table 4: Diagnostic performance and characteristics of maternal HCV RNA (x10^6 copies/mL) in prediction of developing neonatal positive HCV Ab and positive HCV RNA

Conditions	AUC	SE	P	95% CI	Cutoff	Sensitivity	Specificity
Positive HCV Ab	0.749	0.050	<0.001*	0.651–0.847	≥4.7	0.839	0.614
Positive HCV RNA	0.787	0.080	0.007*	0.629–0.944	≥9.2	0.625	0.870

AUC: Area under curve, SE: Standard error, CI: Confidence interval

DISCUSSION

The current research study involved, 100 cases of HCV RNA positive pregnant women were recruited into a cohort study from gestation to 6 months after delivery at Obstetrics and Gynecology department in collaboration with Hepatology, Gastroenterology and infectious diseases department at Benha university hospital from 2016 to 2018. Maternal and child research data were collected via HCV antibody testing and HCV RNA testing.

As regards mean age +/-SD of maternal age(yrs) ,BMI,parity , Maternal RNA (x10^6 copies/mL),gestational age at delivery=31.6+/-2.6yrs, 24.2+/-1.6kg/m2, 2+/-1,6.4+/-3.8 x10^6 copies/mL,39.1+/-1.0 gestational weeks). Concerning maternal exposures dental interventions =23%,operations =23%, transfusions =16%, IV abuse =0%. as regards neonatal exposure amniocentesis=0%, scalp electrode=0%, ROM>6 hours =16 %, cesarean delivery =49%. More than half of neonates had positive Ab (n=56 cases,56 %), and less than tenth of cases had positive RNA. (8%) in which from 100 neonates 44 cases were HCV Ab negative and 56 cases were HCV Ab positive from those 48 cases were HCV RNA negative and 8 cases were positive.

Maternal RNA was highest in Ab +ve/ RNA +ve, (11.0±5.3x10^6 copies/mL) followed by Ab +ve/ RNA –ve (7.3±3.5 x10^6 copies/mL) and least in Ab –ve (4.6±2.7 x10^6 copies/mL)with statistical significant difference between them (*p value*<0.001). ROM >6 hours was highest in Ab +ve/ RNA +ve(10/48,20.8%), followed by Ab +ve/ RNA –ve (3/8, 37.5%)and least in Ab –ve(3/44, 6.8%) with statistical significant difference between Ab +ve/ RNA +ve and Ab –ve research categories (*p value* =0.042). Cesarean delivery was lowest in Ab +ve/ RNA +ve(3/8,37.5%), followed by Ab +ve/ RNA –ve(22/48,45.8%) and highest in Ab –ve(24,54.5%) with no statistical significant difference. (*p value* =0.594).

Statistical logistic analysis have shown that Maternal viral load and ROM >6 hours were statistically significant factors that increase the risk of developing neonatal positive HCV Ab (*p value* <0.001, 0.042, consecutively) and positive HCV RNA (*p value*=0.001, 0.029,consecutively)

Finally diagnostic performance of maternal HCV RNA (x10^6 copies/mL) in prediction of developing neonatal positive HCV Ab and positive HCV RNA have revealed that Maternal HCV RNA had statistically significant low diagnostic performance and characteristics in prediction of developing neonatal positive HCV Ab(AUC =0.749,SE=0.050, *Pvalue*<0.001, 95%CI=0.651–0.847, cutoff ≥4.7, sensitivity =0.839, specificity=0.614) and positive HCV RNA (AUC=0.787, SE=0.080, *P value* =0.007, 95%CI=0.629–0.944, cutoff ≥9.2 sensitivity =0.625, specificity=0.870).

Previous researchers modeled the number of HCV vertical infections based on demographic characteristics of the Egyptian population, epidemiological estimates of HCV prevalence among currently married women in reproductive age, and two separate robust estimates of the risk of HCV vertical transmission.[20-25]

The resulting estimates showed that between 3,000 and 5,000 children in the 2008 birth cohort were vertically infected with HCV. Lower Rural and Upper Rural subnational areas together contributed more than 7 in every 10 incident infections occurring through this mode of transmission in Egypt.[26]

This geographical clustering of HCV vertical infections was largely driven by the combination of higher HCV prevalence and higher fertility rates in these subnational areas. The HCV epidemic in Egypt is of similar scale to the HIV epidemic in sub-Saharan Africa. In this context, all potential transmission routes need to be examined with the view of being addressed by public health interventions.[27]

The national estimate of HCV incidence in Egypt remains contentious, and the relative contributions of the transmission routes that drive this incidence are not well established. To our knowledge, this is the first published study to estimate the contribution of a specific HCV transmission route to HCV incidence in Egypt.[28]

Moreover, this research is also the first to estimate, for any country, the number of HCV infections resulting from vertical transmission. Our estimates of the absolute and relative contribution of vertical transmission to HCV incidence are essential for planning health service provision and development of appropriate interventions. Indirectly, but importantly, our findings show that transmission routes other than mother-to-child transmission contribute the

bulk (>90%) of the overall HCV incidence in Egypt. The relative contribution of each of these remaining routesis yet to be quantified.[29]

In a prior research study study subjects were identified between June 2010 and May 2012 by clinicians during pregnancy or as soon as possible post-delivery, but not later than the child's second birthday. Study inclusion criteria were women aged ≥18 years, pregnant, anti-HCV positive (+/− HCV RNA positive), and able to provide consent for both their own and their child's participation. The exclusion criteria were: maternal HIV and inability to give consent. Age and clinician determined HCV risk history was recorded for non-participating women. Participants were followed up until the child was at least aged 2 years. Research visits were undertaken at baseline (pregnancy and up to delivery); postnatal (2–6 months post-delivery) and followup (18-months to 2-years post-delivery).[30-34]

CONCLUSIONS

Although uncommon, vertically transmitted HCV is most likely to occur, but unlikely to be detected in the current testing environment, in vulnerable children whose mothers have a history of drug injection and poor health-care engagement.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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