Hepatitis C Virus Infection and its Vertical Transmission in a Sample of Egyptian Pregnant Women.

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Abstract: The present study is a cross sectional study performed at Al-Azhar University hospitals (New Damietta and Al-Zahraa) to assess the sero-prevalence rate of HCV among the pregnant females and their neonates. **Methods**: A total number of 300 pregnant women in the third trimester attending at Al-Azhar University Hospitals for labor were randomly selected. All patients were subjected to full history taking and complete general and obstetrical examinations. A venous blood samples were collected from each woman of 3-4 ml blood. Cord blood samples were obtained immediately after birth from babies of the included mothers. The collected venous blood samples were centrifuged, serum was analyzed for hepatitis-C antibody by ACCURATE Cards, and the result was taken in the form of positive versus Negative. **Results**: The results of the present work showed that the prevalence of HCV-Abs in the studied samples of the pregnant females were 8.3%. All the neonates born to HCV-Ab's positive mothers were negative for HCV-Abs at birth. Certain risk factors positively correlated with increased risk of HCV-infection, as history of blood transfusion, previous operation, unsafe injections using non-disposable syringes and high risk occupations.

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1. Introduction:

Hepatitis C virus first identified in 1989 is strictly a blood- borne RNA viral infection of the family Flaviviridae. Humans are the only reservoir for this viral infection **(Miller and Abu-Raddad, 2010).** There are at least 6 major genotypes and more than 50 subtypes of HCV, the different genotypes have different distribution **(Gonik, 2008)**.

Hepatitis C virus infection is a major health problem throughout the world. It is estimated that nearly about one hundred and seventy million people worldwide are HCV virus antibodies positive; of these 35% are women in the childbearing years **(WHO, 2002)**. The World Health Organization (WHO) estimates that 3% of the world's populations are chronically infected with HCV and that it accounts for around 20% of cases of acute hepatitis and 70% of cases of chronic hepatitis, Africa is reported to have the highest HCV prevalence rate **(Madhava *et al.*, 2002).**

Egyptians have the highest prevalence of antibodies to HCV in the world, estimated nationally at 14.7%; an estimated 9.8% are chronically infected. Numerous HCV prevalence studies in Egypt have published various estimates from different Egyptian communities, suggesting that Egypt relative to the other nations of the world might be experiencing intense ongoing HCV transmission **(Miller and Abu-Raddad., 2010).**

HCV is transmitted mostly via infected blood or blood products. Other risk factors include accidental contamination during medical procedures **(Strader *et al.*, 2004).** Perinatal transmission is the major route of infection to the infant. The average rate of infection to infant born to HCV infected mother is 5-6%.The chance of infection has to be greater with higher serum level of HCV-RNA (17%) and in mother co-infected with HIV (14%). It can occur during pregnancy, delivery or postnatally through breast feeding **(Gonik, 2008**).

The potential importance of HCV infection in Egypt has been noticed due to the increased prevalence of HCV antibody seropositivity in normal children attending rural primary schools (12 percent), with a significantly higher prevalence (38 percent) in children with schistosomal hepatic fibrosis **(El-Nawawy *et al.*, 1995).**

Pregnancy does not affect the clinical course of acute or chronic hepatitis C, although several studies have shown improvement in biochemical markers of liver damage in HCV-positive women during pregnancy **(Conte *et al.*, 2000)**.

Standard therapy for the treatment of chronic HCV infection is pegylated interferon and ribavirin

(Fried *et al.*, 2002).Treatment with the most efficacious therapy (pegylated alpha interferon combined with ribavirin) cannot be used during or immediately before pregnancy, because ribavirin poses an important risk of teratogenicity **(Kilham and Ferm., 1977).** Alpha interferon is considered to be contraindicated in pregnancy and children less than 2 years of age as a result of potential neurotoxicity **(Barlow *et al.*, 1999).**

Aim of the work:

Assessment of the prevalence of HCV infection among Egyptian pregnant females attending for delivery at Al-Azhar University hospitals (New Damietta, Al-Zahraa and Assiut), and assessment of the incidence of vertical transmission from mothers to their newborns.

2. Patients and Methods:

This study is a cross-sectional study conducted in Obstetrics and Gynecology Departments of Al-Azhar University Hospitals (New Damietta, Al-Zahraa and Assiut). It included 300 pregnant women when coming in labor.

Inclusion criteria: All pregnant female irrespective to their parity, in labor, with the baby alive.
Exclusion criteria: IUFD.

For each patient the following was done:

1. Full history taking from all patients including: complaint, age, parity, the date of the last menstrual period, past history for surgery or blood transfusion.

2. General examination for:

- Body weight and height.
- Blood pressure was measured in semi-sitting position with standard mercury sphygmomanometer with an appropriate sized cuff
- Lower limbs examination

3. Abdominal examination for estimation of fundal level and auscultation of fetal heart sound.

4. Routine investigations**:** Maternal venous blood samples will be obtained for routine ante-natal investigations.

5. **Blood sample collection:** a venous blood sample was collected from each woman of 3-4 ml blood. Cord blood samples was obtained immediately after birth from babies of the included mothers.

The collected venous blood samples was centrifuged by Beckmancouter; which rotate 3000 cycle/minute and the blood samples lasted for five minutes in the device. The supernatant of both maternal samples and neonatal samples were tested for hepatitis HCV-Antibodies using one step test device (ACCURATE Cards).The ACCURATE Cards are HCV One Step Test Device (Serum/Plasma) is a chromatographic immunoassay for the qualitative detection of antibody to Hepatitis C Virus in serum or plasma.

The HCV One Step Test Device (Serum/Plasma) is a qualitative, membrane based immunoassay for the detection of antibody to HCV in serum or plasma. The membrane is coated with recombinant HCV antigen on the test line region of the device. During testing, the serum or plasma specimen reacts with the Protein-A coated particles. The mixture migrates upward on the membrane chromatographically by capillary action to react with recombinant HCV antigen on the membrane and generate a colored line. Presence of this colored line indicates a positive just, while its absence indicates a negative result. To serve as a procedural control, a colored line will always appear at the control line region indicating that proper volume of specimen as been added and membrane wicking has occurred

Limitations:

1. The HCV One Step Test Device (Serum/Plasma) is for in vitro diagnostic use only. This test should be used for the detection of antibodies to HCV in serum or plasma specimen.
2. The HCV One Step Test Device (Serum/Plasma) will only indicate the presence of antibodies to HCV in the specimen and should not be used as the sole criteria for the diagnosis of Hepatitis C viral infection.
3. As with all diagnostic tests, all results must be considered with other clinical information available to the physician.
4. If the test result is negative and clinical symptoms persist, additional follow-up testing using other clinical methods is recommended. A negative result at any time does not preclude the possibility of Hepatitis C Virus infection.

Expected Values:

The HCV One Step Test Device (Serum/Plasma) has been compared with a leading commercial HCV EIA test. The correlation between these two systems is 98%.

Performance Characteristics:

Sensitivity: The HCV One Step Test Device (Serum/Plasma) has passed a sero-conversion panel and compared with a leading commercial HCV EIA test using clinical specimens.

Specificity: The recombinant antigen used for the HCV One Step Test Device (Serum/Plasma) is encoded by genes for both structural (nucleocapsid) and non-structural proteins. The HCV One Step Test Device (Serum/Plasma) is highly specific for antibodies to Hepatitis C Virus compared with a leading commercial HCV EIA test.

Methods	EIA		Total Results
HCV Test Device	Positive	Negative	
	92	20	112
	3	1888	1891
Total Results	95	1908	2003

Relative sensitivity: 96.8%.Relative specificity: 99.0% Accuracy: 98.9%

Statistical methodology:

- Analysis of data was done by IBM computer using SPSS (statistical Package for social science version 12 (SPSS Inc, Illinois, Chicago, USA).
- For qualitative (categorical data), frequency and percent distribution were calculated and for comparison between groups, the chi square or fisher exact test was used.
- For quantitative data, mean, standard deviation (SD), range (minimum – maximum) were calculated and for comparison between two means, the unpaired (t) test was used.
- For interpretation of results, p value ≤ 0.05 was significant.

3. Results:

Table (1) Distribution of different risk factors for HCV among studied cases

Risk factor		Number	%
Past history of operation		137	45.7
Past history of blood transfusion		44	14.7%
Mode of delivery	NVD	172	57.3%
	C.S.	128	42.7%

This table shows that more than 45% of the studied cases had past history of previous operations, more than 14% had positive history of blood transfusion and more than 42% had history of CS delivery, while NVD was found in 57.6%.

Table (2): incidence of hepatitis C in mothers and babies of studied patients.

HCV mother	No	%
Negative	275	91.7%
Positive	25	8.3%
HCV baby	No	%
Negative	300	100%
Positive	0	0%

This table shows that 8.3% of the studied women had positive HCV results and no vertical transmission of HCV was detected among the newborns.

Table (3) Comparison between negative and positive HCV mothers as regard age and parity

Variables	HCV		*P*
	Negative	Positive	
Age (years) (mean ± S.D)	26.22± 5.11	34.35± 6.25	<0.001
Parity (mean ± S.D)	1.15±1.01	4.21 ± 2.11	<0.001

This table shows that positive group had higher age and parity compared to negative mothers with statistically highly significant difference in between by using unpaired t-test.

Table (4) Comparison between negative and positive HCV mothers as regard past history of surgery

Past history	HCV		*P*
	Negative	Positive	
Negative for surgery	163 (59.3%)	0	
Positive for surgery	112 (40.7%)	25 (100%)	<0.001

This table shows that 100% of positive mothers had a history of previous surgery, while 40.7% of HCV negative patients were positive for surgery with statistically significant association.

Table (5) Comparison between negative and positive HCV mothers as regard past history of blood transfusion

Blood transfusion	HCV		*P*
	Negative	Positive	
No history	252 (91.6%)	4 (16.0%)	
Presence of history	23 (8.3 %)	21 (84%)	<0.001

This table shows that 84.0% of positive mothers had a previous blood transfusion, while 8.3% of negative mothers had positive history of blood transfusion with statistically significant association.

Table (6): Comparison between negative and positive HCV mothers as regard mode of delivery

Mode of delivery	HCV		*P*
	Negative	Positive	
NVD	160 (58.18%)	12 (48.0%)	
CS	115 (41.81%)	13 (52.0%)	**0.32(NS)**

This table showed that, 52% of positive HCV patients were delivered by CS, compared to 41.81% in negative cases with statistically insignificant difference.

4. Discussion:

Hepatitis C virus is a major health problem throughout the world. It is estimated that nearly about one hundred and seventy million people worldwide are HCV virus antibodies positive; of these 35% are women in childbearing years **(WHO Consultation, 2002)**.Egypt is considered one of the countries with the highest prevalence of HCV in the world **(Abdel-Aziz *et al.*, 2000)**.There are some reports claims that vertical transmission is higher in Egypt than other countries **(Kassem *et al.*, 2000)**.

This study is a cross-sectional study was done at the Obstetrics and Gynecology Departments of Al-Azhar University hospitals (Damietta and Al-Zahraa). Depending on the screening of blood samples withdrawn from (300) pregnant women and their neonates immediately after birth. The withdrawn samples were screened for the presence of HCV-antibodies using the ACCURATE cards. The results of this study revealed that the seroprevalence rate of HCV- antibodies among all the tested pregnant females was 8.3%. This rate is high as compared with United States and international studies that reported the seroprevalence rate of HCV-antibodies among the pregnant women to be between 0.7% and 4.4 % **(Delia *et al.*, 2004)**.

This study show that blood transfusion increase the incidence of HCV and this is in agreement with **Sangha *et al.* (2010)** who found that a history of blood transfusion increase the incidence of HCV.

In the present study 21 cases of HCV Ab +ve mothers (84%) receive at least a single blood transfusion or blood product.

Also this is in agreement with study In the United States on 912 people who received transfusions between 1985 and 1991 found that the risk for HCVinfection was 0.45% per unit transfused before donor blood screening began **(Alter *et al.*, 1999)**.

The prevalence of HCV- Antibodies in the present study is 8.3 and this in agreement with study was done at Benha University from October 2003 to July 2008 on 1224 pregnant women. They completed a questionnaire about risk factors for HCV acquisition and suspected risk factors for mother-to-infant transmission and were tested for HCV antibody using a third-generation ELISA test. Women positive for HCV antibody were tested for HCV RNA by polymerase chain reaction. Peripheral blood of infants of positive mothers was tested for HCV antibody and HCV-RNA at 1 and after 6 months of age. Out of 1224 pregnant women, 105 (8.6%) were positive for HCV antibody **(Khaled Abdul Qawi *et al.*, 2010)**.

But this is against study in the year 2000, the department of Pediatrics, Faculty of Medicine, Alexandria University, published a study to assess the prevalence of HCV infection and its vertical transmission in 100 healthy, HIV-negative, Egyptian pregnant women who delivered spontaneously at Alexandria University Hospital and their newborns using third generation ELISA test and PCR of HCV-RNA. Nineteen percent of pregnant women were HCV-seropositive **(Kassem *et al.*, 2000)**.

This study show HCV-Abs positive cases are increased with age which is agreement with **Ketzinel-Gilad *et al.*(2000)**, who found that incidence of HCV increase with age. The increase incidence with the advancement of age may be attributed to increased exposure to other risk factors such as operations and transfusion of blood or blood products.

Also this study show HCV _abs positivecases are increased with gravidity .The increased HCV infection with increased gravidity may be attributed to increased risk of abortion and the need of operative interference and repeated deliveries and this is in agreement with **Einav *et al.* (2002)** who found that repeated deliveries carry the risk for transfusion of blood or blood products increased instrumental delivery, tissue injuries and operative delivery. In this study, history of operation increase the incidence of HCV infection and this in agreement (**Einav *et al.* (2002)** who found that HCV incidence increase by history of operation.

In this studythere were no newborns who had antibody against HCV and this agree with study was done in Southern India that show all newborns were negative for HCV immediately after delivery **(Rudrapathy Parthiban *et al.*, 2009)** and this

against **Tajiri *et al.* (2001)** who performed a study over 16,800 pregnant females to estimate the vertical transmission of HCV and risk factors for transmission. All the pregnant females were screened for HCV-Antibodies, 114 of them were HCV-Antibodies positive. The HCV-Abs positive mothers and their neonates were followed up for 6 months. Of the 114 infants 9 (7.8%) had detectable HCV-RNA. The transmission rate was not influenced by the mode of delivery either vaginal or caesarean or by the type of feeding. All infected infants were born to mothers who had HCV viremia at the delivery and to those with a high viral load.

In 1998, a cohort prospective study enrolled both HCV-seropositive and HIV- sero-negative pregnant females at five obstetric clinics in New York City, to estimate the rate of HCV vertical transmission, the effect of potential risk factors, and pattern of HCV-Antibodies response and viremia in HCV-infected infants. HCV infected mothers and their 122 offspring were followed up for 12 months for evidence of HCV-infection as determined by persistent HCV- Antibodies or detection of HCV-RNA. Seven (6%) of the 122 infants were HCV-infected. There was a tendency for increase transmission with maternal viral and obstetrical factors, such as HIV-coinfection, HCV viremia, vaginal delivery and female gender of offspring **(Granovsky *et al.*, 1998).**

In 2000, **Gibb *et al.*,** evaluated data from 3 hospitals in Ireland and from a British pediatric surveillance study to provide estimates of the rate of mother-to-infant transmission of hepatitis C, and to identify risk factors for transmission of the virus. A total of 441 HCV- infected mothers and their neonates were analyzed longitudinally. The overall rate of vertical transmission of hepatitis C in this study was 6.7%, increasing to 18.6% in mothers co-infected with HIV (i.e. 2.8 times higher). The slow clearance of maternal antibodies in infants born to HCV-infected mothers is highlighted the finding that, half of the uninfected but seropositive children (HCV-Antibodies positive but HCV-RNA negative) became HCV-antibody-negative by 8 months and 95% by 13 months. Conversely, hepatitis C-RNA was identified by polymerase chain reaction (PCR) in only 22% of infected neonates younger than 1 month, but was detected in 97% of infected infants after that time period. No effect of breastfeeding on transmission was observed, although only 59 women breastfed. However, delivery by elective caesarean section before membrane rupture was associated with a lower transmission risk than vaginal or emergency caesarean-section delivery **(Gibb *et al.*, 2000).**

In 2005, two separate studies were done to estimate the vertical transmission of HCV and investigate the effects of mode of delivery and infant feeding on the risk of HCV transmission. First, 244 infants born to HCV- positive mothers from two centers in the United States were followed from birth until age 12 months. Testing was done using ELISA-3, detection of HCV-RNA (qualitative and quantitative), and genotyping. The overall rate of vertical transmission from mothers who were HCV RNA positive at delivery was (4.7) but five times higher in HIV-seropositive females. Membrane ruptures more than 6 hours and internal fetal monitoring were associated with transmission of HCV to infants **(Mast *et al.*, 2005)**

Second, 1787 of HCV- positive mothers from 33 centers in 7 European countries were followed up from birth up to 18 month age. Testing was done using ELISA-3, PCR, and genotyping. The overall rate of HCV- vertical transmission was (6.2%) but higher in HIV-co-infected mothers. Among the women with hepatitis C virus infection-only, multivariate analyses did not show a significant effect of mode of delivery and breastfeeding. Membrane ruptures more than 6 hours and internal fetal monitoring was associated with transmission of HCV to infants **(European Pediatric Hepatitis Network *et al.*, 2005)**.

In this study, mode of delivery was not statistically significant in prevalence of HCV and this agreement with **Gulfareen *et al.* (2009)** who found that mode of delivery was not statistically significant in prevalence of HCV.

All the neonates of the HCV-positive mothers in this study were normal, living and with no congenital fetal malformation. This is in agreement with **Kudo (1997)** who reported no association between maternal HCV-infection with abortions, still births, premature births or congenital fetal malformations.

Conclusions:

- Hepatitis C virus is a major health problem worldwide, as it is the most important cause of chronic liver disease, primary hepatocellular carcinoma and a leading cause of high morbidity and mortality.
- The prevalence of HCV-Antibodies in the studied women 8.3 %.
- All the neonates whom mothers HCV-positive Antibodies were negative for HCV-Antibodies at time of birth.
- History of previous operation was statistically significant as risk factor for HCV infection**.**
- History of blood transfusion was statistically significant as risk factor for HCV infection**.**

- The maternal viral titer appears to be an important determinant of vertical HCV transmission. The higher the concentration of serum HCV RNA, the more likely the chance of vertical transmission.
- Co-infection with HIV has been consistently shown to increase the risk of perinatal transmission of HCV.
- No correlation between HCV genotype and vertical transmission of HCV.
- Breast feeding is generally not considered to be a risk factor for vertical transmission of HCV.
- No a significant association between mode of delivery and vertical HCV transmission.

Recommendations:

- Screening of all pregnant females for HCV infection during the antenatal visits or during labor, especially the patient with positive risk factors.
- PCR should be done for all the HCV-Antibodies positive mothers, because it is the Confirmatory test.
- Infants delivered of mothers known to be HCV positive should be tested for HCV by ELISA or PCR at or shortly after birth and, if negative, the tests should be repeated at 3–6 months.
- Infants whose blood has blood has been found to be positive for HCV by PCR on two occasions should be considered to have been infected,
- WHO and CDC recommendations for prevention of occupational exposure to HCV and other blood borne viruses.
- Strict Methods for prevention and control of HCV infection should be applied

More researches and studies should be done with Long term follow up of HCV-seropositive mothers and their neonates.

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