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Research Article

Hepatitis C Virus Infection during pregnancy in Delta Egypt

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Abstract

Background: Hepatitis C virus (HCV) is one of the major etiological agents for parenteral acquired hepatitis. It is asymptomatic in large proportion of cases (65-75%) and revealed accidentally by abnormal liver function tests or anti-HCV positivity. **Aim:** To assess the prevalence, risk factors and pregnancy outcome of hepatitis C in pregnant women of Delta Egypt. **Study type:** This is a cross sectional study. **Patient & Methods:** A total of 1500 pregnant women that were randomly selected when coming in antenatal care outpatient clinic in Etay El-Baroud general hospital El-Behira governorate of Delta Egypt in the period from the 1st of November 2012 till the end of March 2014 An informed consent obtained from them before inclusion in the study. 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 kit. Women positive for HCV antibody were tested for HCV RNA by polymerase chain reaction. Peripheral blood of infants of positive HCV-RNA women was tested for HCV antibody and infants positive for HCV antibody were tested for HCV RNA by polymerase chain reaction at birth and after 6 months of age. **Results:** Out of 1500 pregnant women, 156 (10.4%) were positive for HCV antibody. Only 123 (8.2%) were positive for HCV-RNA. HCV infection was associated with older age (**p <0.001***), blood transfusion (**p <0.001***), history of previous surgery (**p <0.001***) and parity more than two**<0.001***) Out of 123 infants tested at first month, 85 (69.1 %) were positive for HCV antibody, but only 14 (11.4%) were positive for HCV-RNA at birth. After 6 months, only 5 (4 %) remained positive for HCV RNA. **Conclusions:** The prevalence of HCV in pregnant women in Egypt is lower than previously reported. Risk factors for transmission suggest that there is a correlation between the age and parity of the studied women and the incidence of hepatitis C infection. Hepatitis C virus infection was found more among those women with past history of previous surgery or blood transfusion. Further studies are needed to explore this issue. Incidence of vertical transmission of HCV in Egypt is not more different than in other countries and it plays no role in the high endemicity in Egypt.

Keywords: HCV- Delta Egypt- pregnancy

Introduction

The term "hepatitis" is used to describe a common form of liver injury and simply means "inflammation of the live (1). Hepatitis is acute when it lasts less than six months and chronic when it persists longer (2).

Hepatitis C virus (HCV) is one of the major etiological agents for parenteral acquired hepatitis. It is asymptomatic in large proportion of cases (65-75%) and revealed accidentally by abnormal liver function tests or anti-HCV positivity. The long term morbidity and mortality is due to chronic hepatitis, cirrhosis, hepatocellular carcinoma and liver failure and perinatal transmission of HCV from mother to offspring is relatively low but possible (less than 10%) (3).

HCV is a spherical, enveloped, single-stranded RNA virus belonging to the Flaviviridae family and Flavivirus genus (4). HCV is closely related to dengue and yellow fever viruses. HCV can produce at least 10 trillion new viral particles each day. RNA-dependent

RNA polymerase, an enzyme critical in HCV replication, lacks proofreading capabilities and generates a large number of mutant viruses known as quasispecies. These represent minor molecular variations with only 1-2% nucleotide heterogeneity. HCV quasispecies pose a major challenge to immune-mediated control of HCV and may explain the variable clinical course and the difficulties in vaccine development (5).

HCV is classified into eleven major genotypes (designated 1-11), many subtypes (designated a, b, c, etc.), and based on the genomic sequence heterogeneity(6).

Genotypes 1-3 have a worldwide distribution. Types 1a and 1b are the most common, accounting for about 60% of global infections. They predominate in Northern Europe and North America, and in Southern and Eastern Europe and Japan, respectively. Type 2 is less frequently represented than type 1. Type 3 is endemic in south-east Asia and is variably distributed in different countries. Genotype 4 is principally found in the Middle East, Egypt, and central Africa. Type 5 is almost exclusively found in South Africa, and genotypes 6-11 are distributed in Asia (7).the highest prevalence (15%-20%) has been reported from Egypt (8). The predominant HCV genotype in Egypt is genotype 4a which shows limited response to treatment (9).

The risks are associated with active Schistosomiases, blood transfusion, dental treatment and hospital invasive procedures (10). HCV prevalence has increased considerably over the past decade, yet few surveys have been conducted on national level (11).
HCV is transmitted mainly through contact with blood and blood products with blood transfusions, and sharing of non-sterilized needles and syringes being the main causes of its spread and intravenous drug use is the most common risk factor. However, many other patients acquire HCV without any known exposure to blood or intravenous drug use (12).

HCV infection is infrequently diagnosed during the acute phase of infection and clinical manifestations occur usually within 7 to 8 weeks after exposure to HCV, but the majority of persons have either no symptoms or only mild symptoms (13).

Symptoms of acute hepatitis have been documented and consisted of jaundice, malaise, and nausea but the infection becomes chronic in most cases, and chronic infection is typically characterized by a prolonged period in which there are no symptoms (14).The risk of vertical transmission of HCV appears to be related to the level of viremia in the pregnant mother and not to the route of (15).

Subjects and methods

Site:

The study was conducted in Etay El-Baroud general hospital in El-Behira governorate Egypt an area with irrigated farmlands and surrounded by canals, a feature typical of the Nile delta. It has the characteristics typical of a Lower Egyptian community: a mixture of urban and rural areas, with significant influence of Egyptian traditions and attitudes.

Study design and population

This prospective study was conducted in two stages: the first stage was a cross-sectional study to assess the frequency of HCV in obstetric population and to determine whether various risk factors to HCV could be identified. The second stage was a longitudinal study of the infants of infected women to identify the pregnancy outcome. The study population included all pregnant women coming for antenatal care irrespective to their parity from the 1st of November 2012 till the end of March 2014. It involved 1500 pregnant women that were randomly selected and an informed consent obtained from them before inclusion in the study.

Patient included are all pregnant women coming for antenatal care irrespective to their parity. For each patient the following was done: Careful history taken, general examination for: Body weight and height. Blood pressure was measured, lower limbs examination, abdominal examination for estimation of fundal level and auscultation of fetal heart sound and maternal venous blood samples will be obtained for routine investigations. Venous blood sample was collected from each woman of 3-4 ml blood and screened for HCV antibodies by third generation HCV Elisa kit and anti-HCV positive subjects were tested for: HCV-RNA by RT-PCR. Peripheral blood of infants of positive HCV-RNA women was tested for

HCV antibody and anti-HCV positive infants were tested for: HCV-RNA by RT-PCR at labor and at 6 months of age.

Blood sample collection

a venous blood sample was collected from each woman of 3-4 ml blood, collected in sterile vacutainers, samples stored at 2-8°C for 3 days. Samples needed to be stored for more than 3 days were stored at -70°C.Specimens showing visible particulate matter should be clarified by centrifugation. Fresh serum was used. Risk factors for HCV infection were recorded. This included age, parity more than 2, history of blood transfusion, history of surgical interfernce (including dental, D&C., C.S) and history of hospital admission. Patients excluded were those who had history of liver disease, PET or diabetes mellitus.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0.Qualitative data were described using number and percent. Quantitative data were described using mean and standard deviation for normally distributed data. Comparison between different groups regarding categorical variables was tested using Chi-square test. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agstino test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used.For normally distributed data,comparison between two independent populations was done using independent t-test. Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

Results

Out of 1500 pregnant women, 156 (10.4%) were positive for HCV antibody. Only 123 (8.2%) were positive for HCV-RNA. HCV infection was associated with older age ($p < 0.001^*$), blood transfusion ($p < 0.001^*$), history of previous surgery($p < 0.001^*$) and parity more than two ($p < 0.001^*$) No significant difference was detected as regard the past history of hospital admission between PCR negative and positive pregnant women($p = 0.599$). Out of 123 infants tested at first month, 85 (69.1%) were positive for HCV antibody, but only 14 (11.4%) were positive for HCV-RNA at birth. After 6 months, only 5 (4%) remained positive for HCV RNA. There is no relation between HCV and pregnancy outcome as regard Apgar score and baby weight.

Table (1):HCV Antibodies and HCV PCR.

Mothers	**No.**	**%**
HCV abs +ve	156 / 1500	10.4 %
PCR+ve	123 / 1500	8.2 %
HCV PCR/ HCV Abs	123 / 156	78.8 %

Table (2): Positive HCV PCR According To Age Groups.

Age groups (Years)	**Total study sample No.=1500**	**PCR +ve group / total study sample %**	**PCR +ve group / total PCR +ve %**
A < 20	316	12 / 316 = 3.8 %	12 / 123 = 9.8 %
B 20 – 29	585	31 / 585 = 5.3 %	31/ 123 =25.2 %
C 30 – 39	495	48 / 495 = 9.7 %	48 / 123 =39 %
D 40 and more	104	32 / 104 = 30.7 %	32 / 123 =26%

Table (3): Significance between groups

Groups	P
Group A vs B	0.313
Group A vs C	0.002*
Group A vs D	<0.001*
Group B vs C	0.006*
Group B vs D	<0.001*
Group C vs D	<0.001*

*: Statistically significant at $p \leq 0.05$

Table (4): PCR and risk factors

Risk factor	HCV. PCR (-ve) (N= 1377)	HCV. PCR (+ve) (N= 123)	P
Blood Transfusion	69 (5.0%)	36 (29.3%)	p <0.001*
Hospital Admission	428 (31.1%)	40 (32.5%)	p = 0.599
Previous Surgery	536 (38.9%)	79 (64.2%)	p <0.001*
Parity >2	414 (30.0%)	66 (53.6%)	p <0.001*

Table (5):Vertical transmission at birth.

HCV INFANTS	NO.	%
HCV Abs +ve	85 / 123	69.1 %
PCR +ve	14/ 123	11.4 %

Table (6): Relation between the level of viremia and vertical transmission of hcv from hcv pcr positive mother to infant at birth

Level of viremia	Quantitative PCR	PCR +ve mothers (n=123)	%	PCR+ve infants (n=14)	%
Very low	<10.000 IU/ml	16	13	-	-
Low	10.000 – 100.000	33	26.8	-	-
Intermediate	100.000 _ million	46	37.4	2	14.3
High	Million _10millions	21	17.1	8	57.1
Very high	> 10 millions	7	5.7	4	28.6

Table (7): Fetal positive PCR results at birth and at 6 months.

PCR+ve	No.	%
At birth	14 / 123	11.4 %
At 6 m.	5 / 123	4 %
At 6 m. / At birth	5 / 14	35.7 %

Table (8):Fetal outcome and PCR at birth

Pregnancy outcome	HCV PCR –ve infants No. = (109)		HCV PCR +ve infants No.(14)		(^{FE}p)
	no	%	no	%	
Abnormal APGAR score	9	8.3 %	1	7.1 %	0.021 (1.000)
IUGR	4	3.7 %	_	_	0.531 (1.000)

FE: Fisher Exact test

Discussion

In this study we found the prevalence of HCV Abs. in pregnant women was 10.4 %and HCV PCR positive was 8.2 This is higher than reported (4.2 %) at 2014(16)and at 2010 in Benha university (6.8%) (17)and lower than reported in Alexandria, Egypt (14%) at 2000(18) and (13.8%) at 2002 (19).

In our study universal screening for hepatitis C virus infection among pregnant women was done and not risk-based screening. This is in agreement with that reported that universal antenatal screening for HCV was widely accepted (100%) and demonstrated that risk-based screening alone would have missed 90% of those positive for anti-HCV, most of whom would qualify for free treatment in the Egyptian National Hepatitis C Treatment Program(16)
The age of the included women range from 16 to 48 years, with a mean age 26. The prevalence in this age group was higher than reported in 2010 with a mean age of 25.3 (17), and age was an important risk factor for HCV infection and the majority of cases are more than 30 years.

In our study the prevalence is lower than reported in 2004. This may be explained that patients in previous studies are treated by parenteral anti-schistosoma therapy (PAT) in Egypt from 1960s-1980s. Our study group contained a smaller proportion of PAT-treated than did the studies conducted more than 9 years ago, which may explain the lower prevalence of HCV.

Our study also found a higher rate of infection among older women. This may be partially explained by the differential exposure of these groups to schistosomiasis campaigns in Egypt, and the use of contaminated needles or syringes during treatment campaigns, suggesting that parenteral exposure continues to be a major transmission route for HCV infection in Egypt (20).

Also the prevalence of HCV in Egypt appears to have decreased; our prevalence of 8.2 % is still higher than in other countries such as the USA (3.2%), Taiwan (1.5%), Zaire (6%), and Saudi Arabia (0.6%) (12),(21) and (22). Risk factors for HCV infection Multivariate analysis in this study found many factors associated with HCV infection .Old age was the first independent factor, which suggests the the cumulative effect of exposure to HCV due to the long period of viral exposure over one’s lifetime, as well as exposure to other potential HCV risk factors. Our results are in agreement with reported in 2010(17) and in2009(23)that indicated that HCV is associated with older age, a previous community-based study in Egypt in 2002 has found that older age patients have a higher prevalence of HCV(24).

Parity >2 was a significant risk factor, which suggests the cumulative effect of exposure to HCV. This is against previous studies that showed that HCV is not associated with greater number of pregnancies (23).

Blood transfusion was another risk factor. Many patients in our study had received blood transfusions before blood donors in Egypt underwent routine screening for HCV. These patients also had other risk factors, like hospitalization and major operations. Although blood transfusion is now considered a less important risk factor, it should be considered carefully, especially in a country with such a high prevalence of the disease. In our study blood transfusion represented a risk factor for HCV infection went with that reported in 2010(17), 2009(25), 2000(26)and 2000(18) who stated that history of previous blood transfusion is a significant risk factor for HCV infection.

Newer assays to detect HCV antibodies have reduced the risk of transfusion-associated HCV, yet up to 10% of donors may be seronegative carriers at the time of blood donation (27). Current estimates place the risk of HCV transmission at 1 in 100,000 per unit transfused (28).

Past history of surgical operation constitutes a significant risk factor for hepatitis C virus infection. Our results are in agreement with thatreported in 2010(17).

There is a high seroprevalence rate of anti-HCV antibodies among patients who underwent surgery before (29).The past history of surgical operation was a significant risk for hepatitis C virus infection(19). An infected surgeon can transmit hepatitis C virus infection to patients (30).Before routine testing for hepatitis C virus infection, almost 4% of surgical patients who received blood transfusion became seropositive for hepatitis C virus (31).No significant difference was detected as regard the past history of hospital admission between PCR negative and positive pregnant women. These results are in agreement with that reported in 2010 (17).

Mother-to-infant transmission for HCV: At birth we found that of 123 infants, 85 (69.1%) were positive for HCV Antibodies only 14 (11.4%) were positive for HCV-RNA. We considered this group as HCV-infected infants. This result is comparable with previous studies (13%) at first month of life (17).

We found a relation between the level of viremia and vertical transmission of HCV from HCV PCR positive mother to infant at birth and more than 85 % of vertical transmission occurred with alevel of viremia more than million IU /ml. These results are in agreement with reported that the risk of vertical transmission of HCV appears to be related to the level of viremia in the pregnant mother and not to the route of delivery. The virus does not appear to be transmitted when a woman's titer is < 10^6/mL or is negative(15).

We found that there is no relation between HCV and pregnancy outcome as regard Apgar score and fetal baby weight. These results are in agreement with thatreported in 2005(32).

At 6 months of life we found that of 14 infants only 5 infants (4%) was HCV PCR positive and 9 infants (7.3%) was HCV PCR negative. This is near to that reported in 2010 that found that at 6 months of life, only (3.8%) were positive for HCV-RNA, indicating persistent HCV infection (17).

Another figure for vertical transmission of HCV (4.6%) was reported from Egypt at one year of age at 2009(33),
In 1998 found that overall vertical transmission rate of 6%9(34) andin 2003 reported an overall vertical transmission rate of HCV of 2.7%, and it was higher in HIV co-infected women (5.4%) than in HIV-negative women (2.0%) (15) Andvertical transmission of HCV occurred in 6.8% in HIV-negative women (40).

Vertical transmission of HCV has been documented in several studies. Anti-HCV antibodies cross the placenta and may persist in the infant for up to 15 months. Optimal screening for HCV in the offspring can be done by testing for HCV RNA at 6-12 months of age. Alternatively, HCV antibody screening using a recombinant immunoblot assay can be performed at 18-24 months(35).
Vertical transmission of HCV has been documented in several studies. Anti-HCV antibodies cross the placenta and may persist in the infant for up to 15 months. Optimal screening for HCV in the offspring can be done by testing for HCV RNA at 6-12 months of age. Alternatively, HCV antibody screening using a recombinant immunoblot assay can be performed at 18-24 months (35).

Most infants born to HCV-positive mothers have HCV antibodies in their blood and that we cannot use the presence of these antibodies to diagnose vertical transmission until after 18 months (36).

The risk of vertical transmission of HCV appears to be related to the level of viremia in the pregnant mother and not to the route of delivery and the virus does not appear to be transmitted when a woman's titer is < 10^6/ml (15).
There is a correlation between the risk of vertical transmission of HCV and the maternal viral load. They were the first to quantitate HCV RNA from HIV-negative mothers near delivery. Among all infants born, the risk of HCV transmission was 10%. However, the risk increased to 36% among infants born to women with HCV RNA titers of > 10^6 copies/ml. No woman whose titer was less than 10^4 copies/ml. transmitted the virus to her infant (37).

Previous studies showed that a large proportion of infants were only temporarily positive for HCV-RNA during the first weeks of life and the PCR test should be repeated again at 6 months of life. Studies that do not test infants when they are older as in our study may lead to overestimates of HCV prevalence and this may be the case with community-based study of perinatal HCV transmission in 3 rural Egyptian villages, where the overall HCV prevalence of more than 20% was found (38), (18) and (39).

Frequent clearances of perinatal HCV infection may explain the previous reports of a high incidence of vertical transmission in Egypt. These reports have relied on cord blood samples or PCR results taken only once within a few weeks after delivery. Together with previous studies, the present study lack follow up of infected infants at age of one year of age to confirms that the incidence of vertical transmission of HCV in Egypt is similar to that in other parts of the world, where it varies from 4.5% to 6.0% .and to confirm that vertical transmission does not play a major role in the high endemicity of HCV in Egypt(19).

We recommended that 1-As Egypt has the highest prevalence rate of hepatitis C in the world, routine antenatal testing of all pregnant women for HCV antibodies appear to be of great benefit and should be justified.

2-PCR is not practical as a routine screening test, so it is used as a confirmatory test in cases with positive HCV antibodies.3-Neonates of PCR positive pregnant women should be investigated for HCV antibodies by ELISA and HCV RNA by PCR at 6, 12 and 18 months of age.4-PCR positive neonates should be referred to a neonatologist for management and follow-up.5-Women known to have hepatitis C infection before pregnancy should be counseled about the risks of hepatitis C during pregnancy including the risk of mother-to-child transmission.

6-Pregnant women known to have hepatitis C infection should be referred to a hepatologist for early management and follow-up during pregnancy and after delivery.7-Health care officers should take care at dealing with infected mothers to prevent risk of getting infection with HCV and to limit mother-to-child transmission.8-As Egypt has a high prevalence rate of hepatitis C, further studies are needed to evaluate prevalence, risk factors of HCV in pregnant women and vertical transmission and to reevaluate the importance of routine antenatal testing of all pregnant women for HCV antibodies.9-The risk factors for HCV high prevalence in Nile Delta is associated with age, blood transfusion, parity, previous surgery and hospital invasive procedures so proper sterilization of medical instruments and screening of blood products should be reviewed.10-As HCV can be transmitted from the doctor to his patients HCV PCR positive obstetricians should take care of infecting pregnant women during any surgical procedure.

We believe that our results reliably indicate a change in the prevalence of HCV in Egypt and further studies are needed to address this problem

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