Rising Endogenous Interferon–α and Declining Transaminases during Pregnancy in Egyptian Women with Chronic Hepatitis C

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Abstract  Background and Study Aims: Immunological changes occurring during pregnancy in HCV-infected women that might protect the foetus attract the attention. Aim was to monitor changes in serum levels of endogenous interferon–α (IFN-α) and transaminases (AST &ALT) in Egyptian pregnant women with chronic hepatitis C (CHC).

Patients and Methods: A total of 56 women were studied. Cases group comprised 26 pregnant women with CHC (positive for both anti HCV and HCV- RNA- PCR). Transaminases were assessed in the 3 trimesters while endogenous INF-α was assessed in early 2nd & late 3rd ones. Three control groups were taken 10 women each: pregnant women with negative HCV-Ab, Non pregnant, HCV positive women and Non pregnant, HCV negative groups. Infants born to CHC patients were tested for HCV-RNA-PCR after ≥ 12 months old. 

Results: Transaminases were statistically significant decreasing as pregnancy was progressing in the cases group. Moreover, in the 3rd trimester, cases group had serum transaminases levels comparable to those of healthy pregnant and non-pregnant-women groups without HCV and significantly lower than those of HCV positive non pregnant women. There was a non-significant rise in viral load in early 2nd and late 3rd trimesters in cases group. Serum endogenous INF-α level was significantly increased when measured in late 3rd compared to that in early 2nd trimester. This rise in serum endogenous INF-α level in the 3rd trimester was significant when compared to all control groups. Fortunately, all the examined 26 infants born to CHC mothers had undetectable HCV-RNA-PCR when were older than 24 months. 

Conclusion: Endogenous INF-α progressively rises during pregnancy in CHC patients and this might explain the low rates of vertical transmission and the noticeable reduction in transaminases levels in such patients.

Keywords: endogenous INF, chronic hepatitis C, pregnancy, vertical transmission


1. Introduction

Egypt suffers from the morbidity and mortality of HCV with its resulting cirrhosis and HCC. It has been regarded as an epidemic with an overall anti-HCV antibody prevalence of 14.7% and the number of Egyptians estimated to be chronically infected with HCV is 9.8% [1,2]. Among the groups less often discussed when considering the burden of HCV infection are pregnant women and their infants. Worldwide, the sero-prevalence of HCV in pregnant women is thought to be around 0.15% to 2.4% in the United States and European countries and much higher in countries like Egypt where it is estimated to be as high as 6-9% [3,4,5,6].
virus (15-20%) [10,11,12,13]. This relatively low rate, in comparison to HBV where it may be up to 28% in HBeAg positive mothers, has attracted the attention towards the immunological changes occurring during pregnancy in women with CHC that might protect the foetus [14,15,16].

Studies on the pathogenesis of HCV during pregnancy have been diverse and, in many cases, yielded conflicting results. Studies to examine the timing of foetal transmission suggested inutero transmission, that transmission may occur directly through the placenta with penetration of only few virions, regardless the way of delivery [17,18,19,20].

Maternal factors that have been cited as playing a significant role in HCV –vertical transmission (HCV- VT) are certain HLA types, as well as the presence of HCV-RNA in maternal peripheral blood mononuclear cells [21,22]. The presence of maternal neutralizing antibodies was found to have no role in promoting or protecting against HCV- VT while placental NK cells and endogenous INF-α were claimed to be protective and may explain the relatively low rate of HCV-VT. Moreover, the endogenous production of IFN-α was also suggested to explain the reduction in serum transaminases serum levels that commonly occurs in patients with CHC during pregnancy [8,23,24].

The aim of the present study was to monitor the changes in serum levels of endogenous IFN-α and transaminases (namely, AST and ALT) in pregnant women with CHC, and to a minor extent assess vertically transmitted HCV infection (if any).

2. Patients and Methods

This was a prospective observational, case-control study. Eligible cases attending our outpatient's clinic in Benha university hospital during a period of 6 months was included in our study. Infants born to CHC patients were tested for HCV-RNA-PCR after ≥ 12 months old. All the studied women gave an informed written consent and the study protocol was approved by the Research Ethics Committee of Benha Faculty of Medicine and its University Hospitals.

2.1. Patients

The cases group comprised 26 pregnant women proved to have chronic hepatitis C (positive for anti HCV and HCV- RNA- PCR). Three Control groups were taken and each one comprised 10 women, namely: pregnant women with negative HCV-Ah, non pregnant, HCV-Ah-positive women and non pregnant, HCV-Ah-negative groups.

Patients with the following criteria were excluded from the study: HBSAg positivity, negative HCV-RNA-PCR, history of diabetes mellitus (DM), history of corticosteroids intake within the preceding few months, autoimmune diseases (testing positive for antinuclear or anti smooth muscle antibody in 1: 40 dilution) and history of intake of antiviral drugs for HCV.

2.2. Methods

All the studied women were subjected to detailed history taking (including personal, obstetrics and gynecological history), schistosomiasis, blood transfusion, drug intake and diseases such as TB and/or DM. The following routine laboratory investigations were done for all the studied women: complete blood count (CBC), random blood sugar, serum creatinine, HCV- Ab and HBsAg. Abdominal ultrasonography was also done.

Patients of the cases group were subjected to the following: serum transaminases (AST & ALT) in the 1st, 2nd and 3rd trimesters, serum endogenous interferon-α level in early 2nd and late 3rd trimesters and quantitative HCV-RNA -PCR at early 2nd and late 3rd trimesters.

The control groups underwent assessment of serum transaminases, once (at mid pregnancy for the pregnant group) beside assessment of serum endogenous interferon-α (IFN-α) level once (at mid pregnancy for the pregnant group).

Mother to child transmission was also assessed. Babies born to mothers of the cases group were followed up by the presence of HCV- RNA in their sera after 12 months of age.

2.3. Statistical Analysis

Descriptive statistics were computed for all variables. The results were expressed as means ± SD. To determine the statistical significance of laboratory findings, multiple comparisons were achieved using ANOVA followed by Tukey test as post host test. Throughout these results, the difference between groups is considered non–significant at p value > 0.05, significant at P value (from 0.05 to 0.001), highly significant at P value < 0.001.

3. Results

The mean age of the studied cases group was 27.9 ± 3.8 years. The control groups were matching this age. The cases group (Table 1) comprised 14 primi- and 12 multi-gravida patients, of whom 15 patients (57.7 %) underwent normal vaginal delivery (NVD), while the remaining 11 (42.3 %) got caesarian section (CS). While in the HCV-Ah negative pregnant group, 60% got NVD and 40% got CS. The mean gestational age was similar in both groups (Table 1). Mild microcytic hypochromic anemia was found in the cases group compared to control groups while platelet- and WBCs- counts showed no statistically significant difference (P > 0.05) between the cases group and the 3 control groups (Table 1).

Figure 1. Mean of AST and ALT serum levels in the studied pregnant women (cases) with CHC.
### Table 1. Patient Characteristics in both case and control groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases Group</th>
<th>Control Groups</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnant HCV – positive (n = 26)</td>
<td>Pregnant HCV- Negative (n = 10)</td>
<td>Non pregnant HCV – positive (n = 10)</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>27.9 ± 3.8</td>
<td>29.8 ± 3.9</td>
<td>26 ± 5.2</td>
</tr>
<tr>
<td>Gestational age</td>
<td>38.4 ± 1.9</td>
<td>38.2 ± 2.2</td>
<td>-----</td>
</tr>
<tr>
<td>Hb (gm/dl)</td>
<td>10.92 ± 0.958</td>
<td>11.92 ± 0.97</td>
<td>11.8 ± 0.7</td>
</tr>
<tr>
<td>Platelet</td>
<td>268077 ± 61710</td>
<td>278077 ± 62710</td>
<td>251177 ± 65410</td>
</tr>
<tr>
<td>WBCs</td>
<td>5720 ± 1420</td>
<td>6100 ± 1890</td>
<td>6780 ± 1730</td>
</tr>
<tr>
<td>R.B.S (mg/dl)</td>
<td>94.85 ± 24.506</td>
<td>96.58 ± 25.52</td>
<td>94.85 ± 23.53</td>
</tr>
<tr>
<td>S.Creatinine</td>
<td>0.697 ± 0.1254</td>
<td>0.797 ± 0.13</td>
<td>0.79 ± 0.2</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>23.8 ± 6</td>
<td>25 ± 7.1</td>
<td>69.4 ± 19.8</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>21.5 ± 5.9</td>
<td>25.4 ± 5.4</td>
<td>52.00 ± 14.6</td>
</tr>
<tr>
<td>S.IFN-α (3rd trimester)</td>
<td>39.1 ± 30</td>
<td>16.45 ± 13.6</td>
<td>18.3 ± 7.5</td>
</tr>
</tbody>
</table>

SD= Standard Deviation
P1= significance between pregnant HCV – positive and pregnant HCV- negative groups
P2= significance between pregnant HCV – positive and non-pregnant HCV – positive groups
P3= significance between pregnant HCV – positive and non-pregnant HCV–negative groups

### Table 2. Mean serum transaminases in HCV positive pregnant women during three trimesters

<table>
<thead>
<tr>
<th>Variable</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (U/l)</td>
<td>33.9 ± 7.8</td>
<td>28.6 ± 8.5</td>
<td>23.8 ± 6</td>
<td>0.023</td>
<td>0.000</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>35.2 ± 7.7</td>
<td>28.2 ± 6.2</td>
<td>21.5 ± 5.9</td>
<td>0.001</td>
<td>0.000</td>
</tr>
</tbody>
</table>

SD= Standard Deviation
P1= significance between 1st and 2nd trimesters in cases group
P2= significance between 2nd and 3rd trimesters in cases group.

### Table 3. Serum IFN-α and viral load in pregnant HCV- positive women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early 2nd trimester</th>
<th>Late 3rd trimester</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.IFN-α (pg/ml)</td>
<td>22.1 ± 15.3</td>
<td>39.1 ± 30.0</td>
<td>0.013</td>
</tr>
<tr>
<td>HCV RNA (IU/ml)</td>
<td>265858 ± 293083</td>
<td>315785 ± 564668</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Figure 2. Change of mean serum endogenous IFN-α level in relation to pregnancy duration in the studied cases with CHC

There was a statistically significant decrease in serum transaminases levels as the pregnancy was progressing (Figure 1). There was a significant decrease in serum transaminases in the 2nd trimester compared to the 1st trimester and also there was significant decreases in serum transaminasesin the 3rd trimester when compared to 2nd one. Our results exhibited a statistically non-significant (P = 0.69) increase in HCV-RNA-viral load when assessed in early 2nd and late 3rd trimesters in the cases group (Table 3).

On the contrary to serum transaminases, serum level of endogenous IFN-α exhibited a significant increase, in cases group, as the pregnancy was progressing. The serum endogenous IFN-α level was significantly increased (P = 0.013) when measured in late 3rd trimester (39.1 ± 30.0 pg/ml) compared to that in early 2nd (22.1 ± 15.3 pg/ml) trimester (Table 3 & Figure 2). Endogenous IFN-α level measured in the cases group in early 2nd trimester showed no significant difference when compared to the studied 3 control groups.

The rate of vertical and perinatal HCV transmission among babies born to mothers with CHC was zero as shown by the absence of HCV RNA in the sera of these infants after the age of 12 months. There were no fetal complications occurred in our study apart from one case of premature birth (delivered before 37 weeks of gestation).

### 4. Discussion

Much remains unknown about HCV dynamics during and after pregnancy, as well as in the neonatal period. It is clear that pregnancy induces tremendous physiological changes leading to a modified course of CHC in infected mothers [7].

High IFN levels were reported in pregnant women that could be due to the placental production. During pregnancy, human trophoblasts produce different types of IFN that can be detected in both maternal and fetal blood.

Worldwide, the sero-prevalence of HCV in pregnant...
women is around 0.15% to 2.4% and is much higher in countries like Egypt where it is estimated to be as high as 8.6% [3-5]. The overall rate of mother-to-child transmission for HCV from HCV-infected, HIV-negative, mothers has been estimated around 5% or less [11]. This relatively low rate has attracted the attention towards studying the immunological changes occurring during pregnancy in women with CHC that might protect the foetus [15,16].

The presence of maternal neutralizing antibodies was found to have no role in promoting or protecting against HCV- vertical transmission (VT), while placental NK cells and endogenous IFN-α were claimed to be protective and may explain the relatively low rate of HCV-VT. Moreover, the endogenous production of IFN-α was also suggested to explain the reduction in transaminases serum levels that commonly occurs in patients with CHC during pregnancy [8,23,24].

The current study presented a highly significant progressive decrease (P < 0.001) of serum transaminases, namely AST and ALT, levels during pregnancy. Both were similarly decreasing as pregnancy was progressing. They showed a statistically highly significant progressive decrease (P < 0.001) when assessed in the 1st, 2nd and 3rd trimesters in the studied cases with CHC. Moreover, in the 3rd trimester, pregnant women with CHC had serum transaminases levels comparable to those of the studied healthy pregnant and non-pregnant women without CHC, with no statistically significant difference (P > 0.05). Our studied non-pregnant women who were HCV-Ab positive showed the highest transaminases level and this rise was highly significant (P < 0.001) when compared to that of the cases group in the 3rd trimester and statistically significant (P < 0.05) when compared with that measured in the 1st and 2nd trimesters in the cases group. This comes in agreement with the results given by Gervais et al., 2000 [25]; Veronesi et al., 2007 [26] and Yeung et al., 2007 [27] who reported significant reductions in serum transaminases to reach normal levels near full term in pregnant women with CHC, despite the persistence of viraemia. Paternoster and his colleagues, 2001 [28] who followed up 65 pregnant women with CHC found that transaminases tended toward a reduction from the baseline during the second and third trimesters. However, when their studied group whose AST/ALT were abnormal at the first test was considered, they recorded no significant changes during the follow-up.

The improvement in serum transaminases levels may be attributed to the physiologic changes associated with pregnancy including expansion in plasma volume, high plasma concentrations of estrogen, and changes in immune reactivity resulting in decreased immune-mediated hepatocellular destruction [25,29]. Moreover, Paternoster et al., 2008 [24] concluded that endogenous IFN production might be responsible for the reduction of serum transaminases during pregnancy.

In the present study, there was a statistically non-significant (P > 0.05) increase in HCV-RNA-viral load assessed in early 2nd and late 3rd trimesters in the cases group. This comes in agreement with the results given by Gervais et al., 2000 [25] and Florani, 2009 [30] who told that HCV-RNA levels rise toward the end of pregnancy. This rise may be seen because of the relative suppression of immunity as pregnancy proceeds. Oestrogen was shown to suppress intra-thymic T-cell differentiation while activating the extra-thymic pathways, a phenomenon noted during pregnancy leading to the modulation of cytokines to maintain tolerance of the paternal antigens in the foetus. These would progressively increase the proliferation of HCV resulting in higher HCV RNA titres in the 2nd and 3rd trimesters [7,31].

On the other hand, Lin and Kao, 2000 [32] and Zein et al., 2001[33] reported a statistically significant decrease in HCV-RNA levels in the third trimester, and Romero-Gomez et al., 1998 [34] reported that a few patients in their study got undetectable serum HCV RNA during pregnancy, becoming positive for HCV- RNA again in the postpartum period. While Paternoster and his colleagues 2001 [28] when tested the HCV-RNA load in their studied 65 pregnant women at the 1st, 2nd and 3rd trimester, they failed to show significant changes in viral load during and even after pregnancy and they finally concluded that qualitative PCR should be done once during the pregnancy, but any staging of the liver disease should be taken after delivery and that quantitative HCV PCR testing during pregnancy would be pointless.

In the present study, serum endogenous IFN-α level exhibited inverse relationship to pregnancy duration. Serum endogenous IFN-α level was significantly increased when measured in late 3rd trimester compared to that in early 2nd trimester. This high level in the 3rd trimester was significant when compared to the 3 control groups. On the other hand, the IFN-α level measured in the cases group in early 2nd trimester showed no significant difference when compared to the studied 3 control groups. These findings come in agreement with the results given by Paternoster et al., 2008 [24] who demonstrated that their studied 47 Italian HCV-positive mothers had a significant higher production of endogenous IFN-α compared with either HCV-negative pregnant mothers or HCV-positive non-pregnant mothers [24]. They, in accordance with Ebbesen et al., 1995 [35] and Aboagye-Mathiesen et al., 1996 [9], attributed this high level to the existence of a placental production of IFN-α that could be detected in maternal and fetal blood. They also added that human trophoblast produces different levels of IFN-α with the presence of a high correlation between IFN-α levels in maternal blood and in trophoblast.

Our study showed inverse relation between serum transaminases and serum endogenous INF-α levels in the studied cases group. This goes in agreement with the results got by Paternoster et al., 2001 [28] who added that the endogenous INF-α may be the direct cause of such reduction in transaminases levels.

Serum endogenous INF-α did not significantly affect the HCV- RNA load in our studied pregnant women with CHC. This was the result given by Paternoster et al., 2008 [24] and Florani, 2009 [30] who reported that serum endogenous INF-α level does not correlate with HCV-RNA load in pregnant women with CHC.

No mother to child transmission was observed in the present study. Our finding may be attributed to the relatively small number of the studied cases, as the overall rate of mother-to-child transmission of HCV from HCV-infected, HIV-negative mothers has been estimated around
5% or less [11,12]. Our finding may be explained by the relatively small number of the studied cases.

In conclusion endogenous INF-α progressively rises during pregnancy in patients with chronic hepatitis C and this may be the cause of obvious reduction in transaminases levels in these patients.

References