

## **The effect of hepatitis C on maternal bile acid level and the fetal left ventricular Tei index**

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## Abstract

Hepatitis C (HCV) is a common form of liver disease encountered in pregnancy. The purpose of this study is to evaluate if hepatitis C is associated with elevated maternal serum bile acids and abnormal fetal cardiac function measured by the left ventricular Tei index in the absence of intrahepatic cholestasis of pregnancy. This is a prospective cohort study on pregnant women with hepatitis C seen through Marshall University's high-risk obstetrics clinic from 2013 to 2014. Women with hepatitis C had a laboratory evaluation and an ultrasound on the fetus to calculate the left ventricular Tei index. Demographic information and delivery outcomes were recorded. Seventy-seven participants with hepatitis C were recruited and consented for this study. Sixty-one participants had complete laboratory and delivery information available for analysis. Twenty-one participants had a viral load that was not detectable and forty participants had a detectable viral load. The mean viral load overall was 1943771 IU/mL (SD 4257143). There was no difference in Tei index between detectable and non-detectable viral load, 0.41 and 0.38 respectively ( $p = 0.41$ ). There was no statistical difference in bile acid level between detectable and undetectable viral load, 12 and 8  $\mu\text{mol/L}$  respectively ( $p = 0.05$ ). Hepatic liver disease manifested by elevated hepatitis C viral load or elevated bile acids did not affect the left ventricular Tei index.

## Keywords

cholestasis, fetus, heart, hepatitis C, pregnancy, Tei index

## Introduction

Hepatitis C (HCV) is the most common blood-borne pathogen in the United States.<sup>1,2</sup> It is caused by a single stranded RNA virus in the Flaviviridae family.<sup>3</sup> A recent study in 2015 estimated that 3.5 million people are currently infected with HCV in the United States.<sup>4</sup> Hepatitis C can be transmitted through various modes including bodily fluids, blood, intravenous drug use, needle stick injuries, vertical transmission at birth, sexual activity, or sharing of personal items with infected blood.<sup>5,6</sup> The exact incidence of HCV in pregnancy is unknown as current guidelines recommend risk-factor based screening; it is thought, however, that it affects 1-1.6% of pregnancies and rising.<sup>7-9</sup> There have been suggestions to consider initiation of population-level screening as high rates of poor obstetrical outcomes have been found in prospective cohorts that are HCV positive.<sup>10</sup> In the Appalachia region it has become an increasingly concerning public health issue.<sup>2</sup> According to the CDC, in West Virginia between 2009-2013 reported rates of acute hepatitis C increased by 82%.<sup>11</sup>

Intrahepatic cholestasis of pregnancy affects approximately 1% of pregnancies and is characterized by pruritus and elevated aminotransferases.<sup>12</sup> The pruritus is notable as it is often described specifically on the palms of patient's hands and the soles of their feet. Patients diagnosed with intrahepatic cholestasis of pregnancy are at risk for adverse pregnancy outcomes including meconium stained amniotic fluid, intrauterine fetal demise, post-partum hemorrhage and premature delivery.<sup>13,14</sup> Pregnancies complicated by HCV are at increased risk for being affected by intrahepatic cholestasis of pregnancy (ICP). In a study by Belay et al involving 91 patients with a diagnosis of HCV, 41 of those (45%) were also diagnosed with ICP.<sup>15</sup> Their study also showed significantly higher median viral load when comparing HCV-infected patients

with ICP to HCV-infected patients without ICP (495,000 vs. 8000 copies/mL,  $P < 0.001$ ). Clinically, in patients diagnosed with ICP infection with hepatitis C, some hypothesize that HCV may actually worsen the pruritus in late pregnancy due to increasing levels of estrogen and progesterone.<sup>12</sup>

The Tei index is an ultrasound technique that measures global cardiac function, relying less on anatomy and precise imaging and being independent of heart rate and ventricular geometry.<sup>16</sup> It expresses global function using a ratio incorporating both systolic and diastolic time intervals (Figure I a and b).<sup>17</sup> Through measurement of the Tei index, studies have shown left ventricular dysfunction and myocardial injury in neonates with maternal diagnosis of ICP.<sup>18,19</sup> Cummings et al evaluated the left ventricular Tei index in pregnancies affected by ICP, showing similar results that fetuses affected by ICP had Tei indices that were significantly elevated compared to Tei indices of control fetuses<sup>20</sup>. However, more than half of the pregnancies were also complicated by HCV.<sup>20</sup> It is unknown if the changes seen in the Tei index of these fetuses were due to HCV or ICP, both of which cause liver dysfunction.

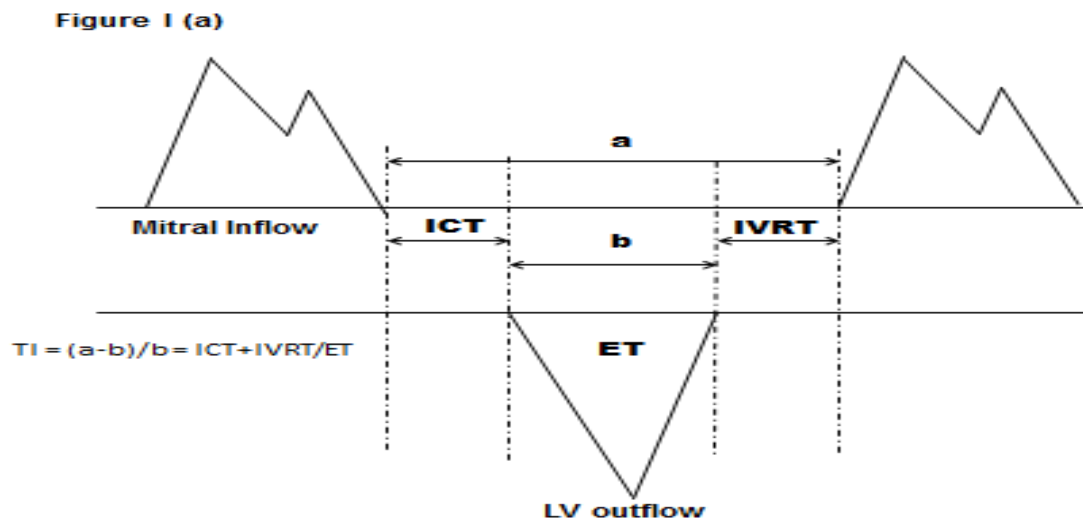
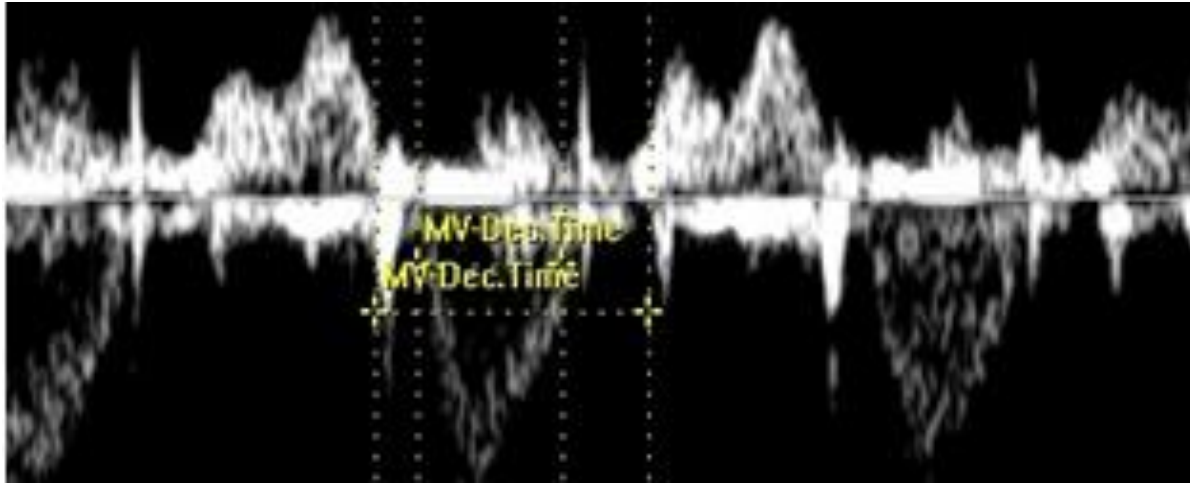


Figure I (b)



There is a growing number of pregnant women being infected with HCV and limited data on the myocardial effects on the fetus. The purpose of this study was to evaluate if hepatitis C is associated with elevated maternal serum bile acids and abnormal fetal cardiac function measured by the left ventricular Tei index in the absence of the diagnosis of ICP.

## Materials and Methods

This is a prospective cohort study on pregnant women with HCV seen through the Marshall University's obstetric high-risk clinic in Huntington, WV from 2013 to 2014. Ethics approval was obtained through the institutional review board. Pregnant women were screened for HCV based on history of substance abuse, current substance abuse/dependence or a positive urine drug screen. A positive HCV screen was followed up with an additional maternal laboratory evaluation (hepatitis C quantitative PCR viral load, liver chemistry panel and fasting serum bile acids). An ultrasound was performed on the fetus to calculate the left ventricular Tei index. The ultrasound studies were performed with a C15 and AB2-7 transducer with 1 of 2 scanners (Voluson 8 and Voluson 730 Expert). One of six registered diagnostic medical sonographers performed the Doppler echocardiography. The medical sonographers routinely perform fetal Tei indices, and the measurements were corroborated by a maternal fetal medicine specialist. Participants were excluded from the study if they had a diagnosis of ICP before enrollment.

All data was summarized by HCV viral load group as the mean and standard deviation for continuous measures and frequency and percentage for categorical variables. Depending on the continuous outcome distribution, statistical analysis utilized either two-sample t-test or Wilcoxon rank-sum test. For binary response, chi-square test statistic or Fisher's exact test was used as appropriate. All analyses were based on a 2-sided test with significance level of 0.05. Pregnancy complications and delivery outcomes were also collected.

## Results

Seventy-seven participants with HCV were recruited and consented for this study. Sixty-one participants had complete laboratory and delivery information available for analysis (Table 1). Twenty-one participants had a viral load that was not detectable and forty participants had a detectable viral load. The mean viral load overall was 1943771 IU/mL (SD 4257143). There was no difference in Tei index between detectable and non-detectable viral load, 0.41 and 0.38 respectively ( $p = 0.41$ ). There was no statistical difference in bile acid level between detectable and undetectable viral load, 12 and 8  $\mu\text{mol/L}$  respectively ( $p = 0.05$ ).

Table 1: Maternal and infant measures

Maternal Measure	Overall (N=61)	Non-Detectable Viral Load (N=21)	Detectable Viral Load (N=40)	p-value
Age (years)	27 (4)	28 (5)	26 (4)	0.22
Gravidity	3 (2)	4 (2)	3 (2)	0.46 <sup>‡</sup>
Parity	2 (1)	2 (1)	2 (1)	0.14 <sup>‡</sup>
<b>Infant Measure</b>				
Gestational age at Tei index (weeks)	32 (4)	33 (2)	32 (5)	0.18
Gestational age at delivery †(weeks)	37 (3)	37 (3)	37 (3)	0.97
Birth weight † (grams)	2925 (739)	2864 (708)	2956 (763)	0.68
Apgar 1 minute †	8 (1)	8 (1)	8 (1)	0.98 <sup>‡</sup>
Apgar 5 minute †	8 (1)	8 (1)	9 (1)	0.26 <sup>‡</sup>
<b>Outcome Measure</b>				
ALT U/L	52 (77)	31 (74)	63 (77)	<0.0001 <sup>‡*</sup>
AST U/L	46 (59)	26 (27)	57 (68)	0.0011 <sup>‡*</sup>
Tei	0.40 (0.11)	0.38 (0.12)	0.41 (0.11)	0.42 <sup>‡</sup>
Bilirubin (mg/dL)	0.44 (0.26)	0.33 (0.08)	0.50 (0.30)	0.01 <sup>‡*</sup>
Bile acids ( $\mu\text{mol/L}$ )	11 (10)	8 (3)	12 (12)	0.05 <sup>‡</sup>

† Denotes measures with missing observations;

‡ Denotes statistical analysis using Wilcoxon rank sum test

Overall the mean alanine aminotransferase (ALT) was 52 U/L (SD 77). Among women with a detectable viral load, the mean ALT was 63 U/L (SD 77) compared to the non-detectable group 31 U/L (SD 74);  $p < 0.0001$ . The mean aspartate aminotransferase (AST) overall was 46 U/L (SD 59); AST in the group with a detectable viral load was 57 U/L (SD 68) compared to 26 U/L (SD 27) in the non-detectable group;  $p = 0.0011$ . The mean Tei index overall was 0.40 (SD 0.11); Tei index in the detectable viral load was 0.41 (0.11) compared to 0.38 (SD 0.08) in the non-detectable group;  $p = 0.41$ .

The ALT, AST, Tei index and bile acids were dichotomized with HCV viral load (Table 2). The normal ALT range for the laboratory used was 12-78 U/L. The ALT was abnormal in 9 (23%)

subjects in the detectable viral load group and 1 (5%) in the non-detectable group;  $p = 0.14$ . The normal AST range for the laboratory used was 15-37 U/L. The AST was abnormal in 14 (35%) subjects in the detectable viral load and 1 (5%) subject in the non-detectable group;  $p = 0.01$ . The Tei index was considered normal if less than or equal to 0.36.<sup>21</sup> The Tei index was abnormal in 23 (58%) subjects in the detectable viral load group and in 12 (57%) subjects in the non-detectable group;  $p = 1.0$ . The bile acids were abnormal in 15 (38%) subjects in the detectable viral load and in 5 (24%) subjects in the non-detectable group;  $p = 0.39$ .

Table 2: Measure of association between ALT, AST, Bile acid, Tei index with HCV VL

Abnormal Outcomes	Overall (N=61)	Non-Detectable Viral Load (N=21)	Detectable Viral Load (N=40)	p-value
Abnormal ALT, N (%)	10 (16%)	1 (5%)	9 (23%)	0.14
Abnormal AST, N (%)	15 (25%)	1 (5%)	14 (35%)	0.01*
Abnormal Tei, N (%)	35 (57%)	12 (57%)	23 (58%)	1.0
Abnormal Bile acids, N (%)	20 (33%)	5 (24%)	15 (38%)	0.39

Note: all analyses were performed using Fisher's exact test

## Discussion

A growing number of pregnant women are infected with HCV and its effect on the fetal myocardium has not yet been fully elucidated. Hepatitis C infection and ICP are both known factors causing liver dysfunction and adverse fetal effects but due to pathologic overlap the management of patients with these diseases can be difficult. Some have simply referred to these disorders as a whole, using the term obstetric cholestasis in the context of several disorders including HCV, acute fatty liver of pregnancy, or adverse drug reactions.<sup>22</sup> Non-invasive antenatal testing and precise diagnosis of the underlying liver disorder should continue to be the goal as an accurate diagnosis can potentially lead to more targeted therapy for both mother and fetus.

An advantage of our study was the final measurement and calculation of the Tei index by a maternal-fetal medicine specialist. By having a single interpreter we were able to consistently reciprocate accurate measurements because of no variability between interpreters. Furthermore, all lab tests were drawn and analyzed at one laboratory, providing good standardization across all patients examined.

This study does have limitations. In the United States, injection drug use is the primary risk factor for HCV infection.<sup>2</sup> As this population has multiple other pregnancy co-morbidities and adverse fetal outcomes it can be difficult to limit confounding variables.<sup>23</sup> Information regarding hepatitis B status, history of cholecystectomy, sub-clinical cholestasis or other processes that could affect serum bile acids levels would further enhance our understanding. Also, we did not differentiate the degree of elevation of the hepatitis C viral load. Future studies could examine the relationship between outcome variables when the viral load is high, greater than 1 million versus low, less than 1 million. The study was also limited by the number of patients. A large,

multi-center prospective trial would enhance our understanding of the effects of hepatitis C virus on the fetal heart.

Fetal heart function, measured by the left ventricular Tei index, may be affected by hepatitis C in pregnancy. The findings from this study warrant further evaluation in a prospective study with a control group. Liver disease in pregnancy manifested by hepatitis C may not be benign in the fetal myocardium.

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