



Fetal TEI Index in Pregnancies with Intrahepatic Cholestasis of Pregnancy: A Case-Control Study

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Abstract

Objectives First, to explore differences in fetal cardiac function in patients with and without intrahepatic cholestasis of pregnancy (ICP) based on the TEI index. Second, to explore a potential correlation between TEI index and bile acid levels in pregnant women with ICP. Third, to study changes in the TEI index of fetuses from pregnant women with ICP after administration of ursodeoxycholic acid (UDCA).

Study Design This is a prospective observational case-control study conducted at Hospital Clínico San José and Clínica RedSalud Vitacura, both in Santiago, Chile, between April 2018 and October 2020. ICP was defined as palmar-plantar pruritus of nocturnal predominance for more than 1 week associated with a total bile acid level above 10 $\mu\text{mol/L}$. Control cases were women with pregnancies scheduled for induction or elective cesarean section between 37 and 40 weeks of gestation according to current protocols. Differences in the TEI index between cases and controls were assessed by the Wilcoxon test. The correlation between the TEI index and bile acid levels was assessed by the Spearman correlation test. Changes in TEI index before and after administration of UDCA were analyzed by the paired samples Wilcoxon test.

Results A total of 181 pregnant women were included in the study, 109 women with ICP and 72 controls. The median gestational age at inclusion was 35.9 weeks (interquartile range [IQR], 33.0–38.9). The median TEI index was 0.31 (IQR, 0.29–0.36); this was significantly longer in fetuses of women with ICP ([0.34, IQR, 0.30–0.38] vs. [0.30, IQR, 0.28–0.31], $p < 0.001$). There was a significant correlation between bile acid levels and TEI index (0.584, $p < 0.001$). In 21 fetuses, the TEI index was measured a second time, 2 weeks later, following UDCA administration. The median TEI index

Keywords

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decreased significantly following UDCA administration (0.40 ms before treatment [IQR, 0.36–0.42] vs. 0.33 after treatment [IQR, 0.32–0.38], $p = 0.001$), $p = 0.001$).

Conclusion The TEI index is increased in fetuses of women with ICP. TEI index was significantly correlated with bile acid levels, and administration of UDCA significantly reduced the TEI index.

Key Points

- Significant correlation between TEI index and bile acid levels.
- Effect of UDCA treatment.
- clinical implications for monitoring and treatment.

Intrahepatic cholestasis of pregnancy (ICP) is the most common disease of the liver during pregnancy and is characterized by predominantly nocturnal itching on the palms of the hands and soles of the feet, the onset is typically during the third trimester of pregnancy. The prevalence varies between 1 and 5%, depending on the geographic area, Chile has one of the highest prevalences of ICP. Has associated, depending on severity, 1 to 4% of unexplained fetal deaths. This is why multiple hypotheses have been investigated, the most recent of which suggests that there is a change in the fetal cardiac rhythm or function.

In recent years, the impact of bile acids on the fetal heart has received particular attention. This is primarily due to evidence showing alterations in myocardial conductivity. Studies in both animal models and recent human research have demonstrated that bile acids can modify myocardial functionality.

As early as 1987, Binah et al¹ demonstrated in their study that an increase in bile acid levels decreases the duration of the action potential in rat cardiomyocytes. This study also established that the effects of bile acids on cardiac function can be direct or indirect. The direct effects include alteration of calcium channels, reduction of intracellular adenosine monophosphate (cAMP), and increased apoptosis through the interaction of bile acids with muscarinic receptors. Indirect effects are related to bile acids and cholesterol metabolism, regulation of blood cholesterol levels, atherosclerotic plaque formation, and myocardial function. Years later, around 2002, another study conducted by Gorelik and colleagues² in experimental rat models demonstrated that elevated levels of bile acids were associated with a decrease in contraction amplitude, a reduction in cardiomyocyte synchronization, and a shorter action potential duration. In 2009, Zhang et al³ studied the correlation between bile acid levels and cardiac dysfunction in neonates. They found that left ventricular TEI index and cardiac troponins were significantly higher in female infants with cholestasis compared to those of the control group. Subsequent studies, which will be discussed in more detail later, have concluded that there are structural and functional changes present in the myocardium of fetuses from pregnant women affected by the condition when compared with fetuses of healthy pregnant women.

Our study had three objectives: First, to explore the difference in fetal cardiac function in patients with and without ICP by comparing TEI index; second, to explore a potential correlation between TEI index and bile acid levels in pregnant women with ICP; and finally, to study changes in TEI index in fetuses of pregnant women with ICP after administration of UDCA.

Materials and Methods

Study Design and Ethics Committee Approval

This was a prospective observational case-control study conducted in Hospital Clínico San José, and Clínica RedSalud Vitacura, both in Santiago, Chile, between April 2018 and October 2020.

The study was approved by the “Comité de ética de la Investigación del Servicio de Salud Metropolitano Norte” on July 19, 2018 (Carta No 052/2018). Written consent was obtained from all participating women.

Study Population

The study population included pregnant women attending the aforementioned hospitals. Inclusion criteria were mothers aged 18 years or older, cases diagnosed with ICP during pregnancy, and controls without ICP symptoms. For these cases, ICP was defined as palmoplantar itching lasting more than a week, mainly at night, and was associated with total bile acid levels greater than 10 $\mu\text{mol/L}$.⁴ Control cases were pregnant women scheduled for induction of labor or elective cesarean delivery between 38 and 40 weeks of gestation according to the current protocol. Exclusion criteria were twin or multiple pregnancies, fetal malformation, fetal growth restriction, maternal viral infection altering maternal liver function, drug therapy affecting maternal liver function or fetal heart function, fetal structural heart abnormality or arrhythmia, and the presence of anti-Ro or anti-La antibodies.

Clinical Protocol

1. Informed consent

During the informed consent process, all pregnant women participating in the study, whether in the ICP group or

the control group, received written information on the pathology and the diagnostic methods used.

2. Bile Acid Measurements

In the ICP group, bile acid measurements were performed when patients were clinically diagnosed with ICP. In severe forms of the disease, this measurement was taken weekly until the end of pregnancy, and in mild form every 2 weeks. Severity criteria were set for this purpose as TBA > 40 $\mu\text{mol/L}$ and/or total bilirubin > 1.8 mg/dL and/or transaminases greater than twice the upper cut-off value established by the clinical laboratory.

In the control group, bile acid measurements were performed at preoperative examination or on admission.

3. Measurement of TEI index

Fetal functional echocardiography was performed at diagnosis and repeated weekly in the severe cholestasis group, at 34 to 36 weeks of gestation in the mild cholestasis group, and at the time of preoperative test or hospital admission in the control group.

The TEI Index was obtained from the Left Ventricular outflow tract plane. In this projection, the mitral and aortic valves can be visualized simultaneously, thus, the isovolumic contraction time, isovolumic relaxation time, and ejection time (ET) can be measured in the same cardiac cycle. This avoids the inaccuracies resulting from measuring time intervals in different cardiac cycles. To do this, the pulsed Doppler sample is placed in the LV at the junction of the anterior leaflet of the mitral valve and the LV outflow tract.

TEI index was measured as follows: from the end of the A-wave to the onset of the aortic pulsed Doppler tracing (ICT), from the onset to the end of the aortic pulsed Doppler tracing (ET), and from the end of the ET to the onset of the E-wave. A single-blinded operator assessed the fetal hearts in the absence of fetal and/or breathing movements. The TEI Index was calculated from an average of the three successive measurements of each of the intervals measured including fetal heart rate.⁵

4. Use and control of ursodeoxycholic acid (UDCA)

UDCA at 15 mg/kg/day divided into 3 to 4 doses was given to all patients diagnosed with ICP. Dosing began after samples were collected for bile acid measurements and fetal echocardiography was performed. Fetal echocardiography was performed again before delivery in this group.

5. Monitoring and end of gestation

In addition, in the mild ICP group, weekly monitoring with cardiotocography (CTG) and liver tests was planned according to the current protocol. In the severe cholestasis group, patients were hospitalized, differential diagnosis was performed, CTG and liver tests were monitored every 48 hours, and bile acids and PR intervals were measured weekly (as previously described). According to the national protocol, pregnancy was terminated at 36 weeks in cases of severe ICP and at 38 weeks in cases of mild ICP.

Study Size

The sample size necessary to achieve our primary outcome (difference in TEI interval) was calculated, and the results of

the Henry and Welsh study were taken into consideration, in which the difference in the TEI index between the high bile acid group and the low bile acid group was 0.04 ms. Accepting an α risk of 0.05 and a β risk of 0.2 in a bilateral contrast test, 45 subjects in the first group and 45 subjects in the second group were required to detect a difference equal to or greater than 0.04 units. The common standard deviation was assumed to be 0.06. A loss to follow-up rate of 20% was estimated.

Outcomes

The main outcome is the TEI index, defined as (isovolumetric contraction time [ICT] + isovolumetric relaxation time [IRT])/ET (→ Fig. 1).⁶

Bile acids were measured from maternal plasma and reported in $\mu\text{mol/L}$.

Statistical Analysis

First, maternal demographic data were analyzed. The distribution of continuous data was tested by the Shapiro test. Normally distributed data were reported as the mean and standard deviation (SD), and nonparametric data were reported as the median and interquartile range (IQR). Categorical data were reported as absolute and relative frequencies (percentages).

Second, demographic, cardiac, and delivery data were compared between cases and controls. Continuous data were compared using the independent samples *t*-test or the Wilcoxon test, depending on whether the distribution was normal or not. Categorical data were compared using the chi-squared test or Fisher's exact test, as appropriate.

The correlation between the TEI index and bile acid levels was investigated using the Spearman correlation test.

Changes in TEI index before and after administration of UDCA were analyzed using the paired samples Wilcoxon test.

Gestational age as a confounder. Gestational age at the time of measurement of the TEI index was examined as a confounding variable. Multiple regression analysis was planned to adjust for the effect of gestational age.

Results

A total of 182 women were included in the study: 110 cases and 72 controls. One hundred and sixty-four (90.1%) women were recruited in Hospital San José, and 18 (9.9%) in Clínica RedSalud Vitacura. All controls were recruited in Hospital San José. The TEI index could not be assessed in one of the fetuses and was excluded. One hundred and eighty-one women were included in the analysis, 109 cases and 72 controls. Bile acid levels were measured in all 181 patients.

Maternal Demographic Data

The median maternal age was 28 years old (IQR, 23–34). Median body mass index (BMI) was 28 kg/m^2 (IQR, 24–31). Regarding nationality, 169 (93.4%) women were Chilean, 8 (4.4%) women were Peruvian, 2 (1.1%) women were Bolivian, and 2 (1.1%) women were Venezuelan. Median gestational age at inclusion was 35.9 weeks (IQR, 33.0–38.9). The

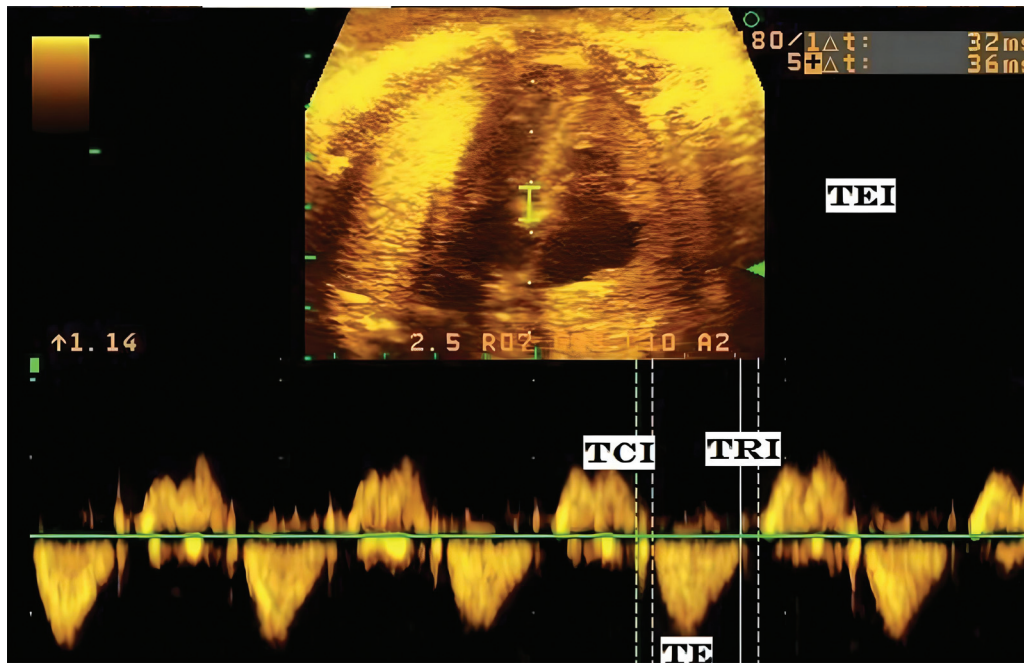


Fig. 1 Measurement of TEI index at the mitral-aortic valves, in a 5-chamber view.

Table 1 Maternal demographic characteristics in intrahepatic cholestasis of pregnancy and controls			
	Intrahepatic cholestasis of pregnancy (n = 109)	Controls (n = 72)	p-Value
Maternal age (y)	28.0 (23–34)	28.5 (23–38)	0.197
Body mass index (kg/m ²)	28 (25–31)	27 (23–31)	0.412
Nationality			
Chile	102 (93.6%)	67 (93.1%)	0.313
Bolivia	2 (1.8%)	0	
Peru	5 (4.6%)	3 (4.2%)	
Venezuela	0	2 (2.8%)	
Gestational age at inclusion (wk)	33.7 (31.5–35.6)	39.0 (38.6–39.4)	<0.001

Note: Continuous data are reported as the median and interquartile range. Categorical data are reported as absolute values and percentages. Comparison between groups was performed using the Wilcoxon test for continuous data and the Fisher's exact test for categorical data.

demographic characteristics of cases and controls are summarized in ►Table 1.

Primary Outcome

The median TEI index was 0.31 (IQR, 0.29–0.36), and it was significantly larger in fetuses of women with ICP (0.34, IQR, 0.30–0.38) as compared with controls (0.30, IQR, 0.28–0.31; $p < 0.001$).

Secondary Outcome 1

In the ICP group, there was a significant correlation between bile acid levels and TEI index ($\rho = 0.584$, $p < 0.001$; ►Fig. 2).

Additionally, in the ICP group, there was a significant correlation between the TEI index and aspartate aminotransferase (AST; $\rho = 0.236$, $p = 0.013$) and between PR interval and alanine aminotransferase (ALT; $\rho = 0.195$, $p = 0.042$).

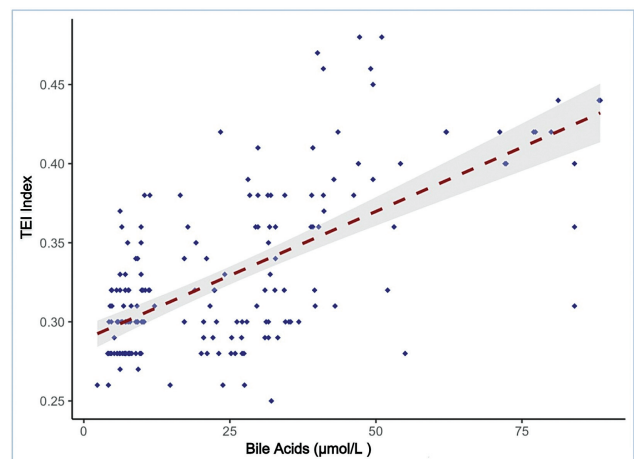


Fig. 2 Correlation between fetal TEI index and maternal bile acid levels in women with intrahepatic cholestasis of pregnancy.

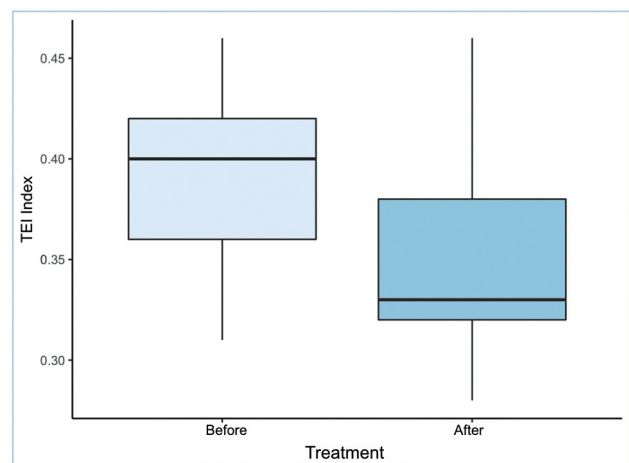


Fig. 3 TEI index before and after treatment with ursodeoxycholic acid.

Secondary Outcome 2

In 21 fetuses, the TEI index was measured a second time, 2 weeks apart, following UDCA administration. The median TEI index decreased significantly following UDCA administration (0.40 ms before treatment (IQR, 0.36–0.42) vs. 0.33 after treatment (IQR, 0.32–0.38, $p = 0.001$; ▶Fig. 3).

Delivery

In this study, the median gestational age at birth was 38 weeks (IQR, 37.1–38.9). One hundred and twenty-four (68.5%) women underwent a vaginal delivery, and 57 (31.5%) women had a cesarean section. Median birthweight was 3,029 g (IQR, 2,870–3,400). One hundred and seven (59.1%) fetuses were male and 74 (40.9%) fetuses were female. Median Apgar score at 1 minute was 9 (IQR, 8–9), and at 5 minutes was 9 (IQR, 9–9). Perinatal outcomes in women with ICP and controls are compared in ▶Table 2. Women with ICP delivered significantly earlier and had babies with a lower birth weight.

Discussion

Main Findings

In this study, we found that the TEI index is significantly greater in fetuses of women with ICP as compared with controls. There was also a significant correlation between the TEI index and bile acid levels. Moreover, the TEI index was shorter following the UDCA administration in women with ICP.

Comparison with Previous Studies

A search for human fetus studies on cholestasis and the TEI index yielded limited results. In the first study published in 2014, Fan et al⁷ did a case-control study in humans to investigate eventual fetal myocardial deformation in patients with cholestasis (40 with ICP, and 40 controls). In this study, a decrease in left ventricular overload was demonstrated in direct correlation with the level of bile acids. Fetal myocardial deformation is impaired in severe ICP. In our study, we decided to use the TEI index as the most clinically reproducible in our local environment. This index also showed a direct relationship with bile acid levels, as did myocardial deformation. In 2016, Ataalla et al⁸ published another study in humans showing that women with cholestasis and high levels of bile acids (>40 mmol/L) present fetal cardiac dysfunction, using tissue Doppler at the fetal myocardium level. In the same year, Henry et al⁶ demonstrated that the fetuses of pregnant women with cholestasis present a significant increase in ventricular isovolumetric contraction and relaxation times compared with the control group. Comparing these two studies with our own findings, a clear correlation has been established between fetal myocardial functionality and total bile acid levels. In 2022, Rodriguez et al⁹ demonstrated that fetuses affected by maternal ICP are associated with electrical and diastolic myocardial dysfunction. Forty-nine patients were included in each group and ICT, ET, and IRT for electrical, systolic, and diastolic function, respectively were measured. IRT was significantly higher in ICP, with no

Table 2 Obstetric outcome in women with intrahepatic cholestasis of pregnancy and controls			
	Intrahepatic cholestasis of pregnancy (n = 109)	Controls (n = 72)	p-Value
Gestational age at delivery	38.0 (37.1–38.9)	39.0 (38.6–39.4)	<0.001
Mode of delivery			
Vaginal	76 (69.7%)	48 (33.3%)	0.787
Cesarean section	33 (30.3%)	24 (66.7%)	
Birth weight	2,915 (2,703–3,090)	3,400 (3,076–3,577)	<0.001
Gender			
Female	46 (42.2%)	28 (38.9%)	0.772
Male	63 (57.8%)	44 (61.1%)	
Apgar at 1 min	9 (8–9)	9 (8–9)	0.897
Apgar at 5 min	9 (9–9)	9 (9–9)	0.893

Notes: Continuous data are reported as the median and interquartile range. Categorical data are reported as absolute values and percentages. Comparison between groups was performed using the Wilcoxon test for continuous data and the Fisher's exact test for categorical data.

differences in ICT and ET. While it is true that the results are similar to those obtained in our study, the work of Rodriguez does not consider the association with bile acid levels.

Finally, the PROSPERO study,¹⁰ a meta-analysis aimed at correlating adverse perinatal outcomes with biochemical markers, concluded that bile acid levels above 100 $\mu\text{mol/L}$ correlate with adverse perinatal outcomes. These elevated bile acid levels were not obtained in our sample group. However, the PROSPERO study does not specify the causes of adverse perinatal outcomes, which is one of the findings of our study.

Clinical Implications

Clinical implications are related mainly to the management of patients with ICP and complement what was published by this same group last year about the evaluation of the PR interval in these patients.¹¹

On the one hand, we have observed that in the fetus, the TEI index is greater when maternal bile acid levels are higher. Therefore, cases with high levels of bile acids may be at a higher risk for adverse perinatal outcomes and should be monitored more closely.

On the other hand, we have observed that treatment with UDCA reduces the TEI index in the fetus, which may potentially imply a reduction in the risk of adverse perinatal outcomes.

Strengths and Limitations

In our study, we did not observe bile acid levels above 100 $\mu\text{mol/L}$. Based on the latest reviews, higher values of bile acid levels are associated with very poor outcomes. Increasing sample size with multicenter studies and correlating the TEI index with the different parameters mentioned in this study may help to identify a correlation between TEI Index/myocardial function and poor obstetric outcomes.

Conclusion

Our study confirms that the TEI index is greater in fetuses of women with ICP. Even more interestingly, the findings of our study show that the TEI index is significantly correlated with bile acid levels. In addition, the administration of UDCA reduced the TEI index significantly.

Funding

None.

Conflict of Interest

N.M. is a member of the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA) EU Framework Partnership (agreement ID: 3HP-HP-FPA ERN-01-2016/739516).

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