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CLINICAL AND FUNCTIONAL ASSESSMENT OF THE LIVER AND PLACENTA USING ELASTOGRAPHY IN PREGNANT WOMEN WITH DRUG-INDUCED LIVER INJURY

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Resume. *The aim of the study was to evaluate the clinical and functional state of the liver and placenta in pregnant women with drug-induced liver injury (DILI) using liver and placental elastography, as well as biochemical markers of liver dysfunction.*

Materials and methods. *The study included 98 pregnant women with DILI in the second and third trimesters and 40 pregnant women with physiological pregnancy. All patients underwent biochemical blood analysis, ultrasound examination, Doppler assessment, and elastography of the liver and placenta. Liver stiffness (LSM), controlled attenuation parameter (CAP), as well as placental parameters (Emean, Emin, Emax, and heterogeneity index Emax/Emin) were evaluated.*

Results. *In patients with DILI, liver stiffness increased to 11.8±2.4 kPa compared to 5.8±1.3 kPa in the control group ($p<0.001$), and placental stiffness increased to 24.6±4.8 kPa versus 14.2±2.9 kPa ($p<0.001$). Significant hyperenzymemia was observed: ALT 98.4±32.6 U/L, AST 84.7±28.1 U/L, and total bilirubin 28.5±9.4 μmol/L. The incidence of placental insufficiency was 62.2% versus 12.5% in the control group; OR=11.54; 95% CI 4.15–32.07. At placental stiffness >25 kPa, the risk of placental insufficiency increased 4.56-fold (95% CI 1.80–11.59).*

Conclusion. *Liver and placental elastography is an informative non-invasive tool for risk stratification in pregnant women with DILI and can be used for early detection of placental dysfunction and adverse perinatal outcomes [11–18].*

Keywords: *drug-induced liver injury, pregnancy, liver elastography, placental elastography, placental insufficiency, ALT, AST, CPR.*

Introduction. Drug-induced liver injury (DILI) is among the most challenging types of hepatic dysfunction to diagnose, as it can mimic a wide spectrum of hepatobiliary diseases and often lacks specific biomarkers. Current guidelines from EASL, AASLD, ACG, and APASL emphasize the importance of a comprehensive assessment of clinical manifestations, laboratory patterns of injury, and the exclusion of alternative causes of liver damage [1–5].

During pregnancy, the interpretation of liver dysfunction is particularly complex due to physiological changes in metabolism, hemodynamics, and laboratory parameters, as well as the need to simultaneously assess maternal and placental-fetal risks. In pregnant women, DILI may be associated not only with cytolytic and cholestatic syndromes but also with secondary impairment of placental perfusion [6–10].

Liver elastography enables quantitative assessment of hepatic tissue stiffness, while placental elastography evaluates the mechanical properties of the placenta, indirectly reflecting microcirculatory and structural changes in the villous tree. Previous studies have demonstrated that in complicated pregnancies, placental stiffness increases and correlates with Doppler signs of placental insufficiency [11–18].

Aim of the study. To determine the clinical, biochemical, and elastographic characteristics of the liver and placenta in pregnant women with DILI and to assess their association with placental insufficiency.

Materials and methods. This study was designed as a prospective comparative cohort study. The main group included 98 pregnant women in the second and third trimesters with clinical and laboratory signs of drug-induced liver injury. The control group consisted of 40 pregnant women with physiological pregnancy and no liver or placental pathology.

Inclusion criteria: gestational age 22–36 weeks; singleton pregnancy; presence of hyperenzymemia associated with the use of potentially hepatotoxic drugs; absence of viral, autoimmune, and mechanical causes of liver injury.

Exclusion criteria: pre-existing chronic liver disease prior to pregnancy; multiple pregnancy; severe preeclampsia at the time of enrollment; fetal congenital anomalies.

Biochemical analysis included ALT, AST, total and direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total protein, albumin, and international normalized ratio (INR).

Liver elastography was performed in the fasting state in the right hepatic lobe with subsequent calculation of liver stiffness measurement (LSM) and controlled attenuation parameter (CAP). Placental elastography was performed in the central and peripheral regions of the placenta with assessment of Emean, Emin, Emax, and the heterogeneity index (Emax/Emin).

Doppler assessment included pulsatility index (PI) of the uterine arteries, umbilical artery, and middle cerebral artery, as well as the cerebroplacental ratio (CPR). Placental insufficiency was defined as the presence of uteroplacental and/or fetoplacental blood flow impairment, or CPR <1.08, or fetal growth restriction.

Statistical analysis was performed using comparative analysis of means, the χ^2 test, and calculation of odds ratios (OR) with 95% confidence intervals. A p-value <0.05 was considered statistically significant.

Results. The mean age of patients in the main group was 29.8±5.4 years, and in the control group 28.9±4.8 years (p=0.36). Gestational age at the time of examination was 31.4±3.6 and 30.9±3.5 weeks, respectively (p=0.48).

Clinically, patients in the main group more frequently presented with asthenovegetative symptoms, pruritus, heaviness in the right upper quadrant, and dyspeptic complaints.

In the main group, marked hyperenzymemia with a predominance of the cytolytic pattern, moderate hyperbilirubinemia, and signs of impaired hepatic synthetic function were observed. The most sensitive laboratory indicators in patients with DILI were ALT, AST, and albumin.

Table 1.

Biochemical Parameters of Liver Function

Indicator	Main group, n=98	Control group, n=40	P
ALT, U/L	98,4 ± 32,6	26,3 ± 7,4	<0,001
AST, U/L	84,7 ± 28,1	24,8 ± 6,1	<0,001
Total bilirubin, µmol/L	28,5 ± 9,4	12,1 ± 3,6	<0,001
Direct bilirubin, µmol/L	12,6 ± 4,2	3,8 ± 1,1	<0,001
ALP, U/L	278 ± 65	182 ± 44	<0,001
GGT, U/L	76 ± 24	28 ± 9	<0,001
Total protein, g/L	63,4 ± 5,1	70,2 ± 4,3	<0,001
Albumin, g/L	32,8 ± 3,6	38,6 ± 3,4	<0,001
INR	1,12 ± 0,12	0,96 ± 0,08	<0,001

In the present study, pregnant women in the main group demonstrated significant alterations in both biochemical and elastographic parameters compared to the control group.

A marked increase in liver stiffness was observed, with values exceeding 9.5 kPa in 67 (68.4%) patients of the main group, indicating a high prevalence of hepatic involvement in DILI during pregnancy (Tab.2).

Placental elastography revealed a substantial increase in placental stiffness in the study cohort. Specifically, placental stiffness values >25 kPa were detected in 42 (42.9%) patients with DILI, whereas only 3 (7.5%) cases in the control group exhibited similar findings. This difference suggests a strong association between DILI and placental tissue remodeling.

These findings indicate that both liver and placental stiffness parameters may serve as valuable non-invasive markers for assessing the severity of maternal hepatic dysfunction and its impact on placental function.

Table 2.

Liver and placental elastography parameters

Indicator	Main group, n=98	Control group, n=40	P
Liver stiffness (LSM) kPa	11,8 ± 2,4	5,8 ± 1,3	<0,001
CAP, dB/m	238 ± 42	198 ± 35	<0,001
IQR/median LSM Placental stiffness (Emean), kPa	0,18 ± 0,05	0,12 ± 0,03	0,002
Emin, kPa	24,6 ± 4,8	14,2 ± 2,9	<0,001
Emax, kPa	17,3 ± 3,4	10,6 ± 2,2	<0,001
Emax, kPa	29,8 ± 5,1	18,5 ± 3,6	<0,001
Heterogeneity index (Emax/Emin)	1,72 ± 0,21	1,45 ± 0,18	<0,001

The analysis of Doppler parameters demonstrated significant differences between the DILI and control groups, reflecting pronounced placental dysfunction in patients with drug-induced liver injury (Tab.3).

Specifically, the pulsatility index (PI) in the uterine arteries was significantly higher in the DILI group compared to the control group (0.92 ± 0.16 vs 0.71 ± 0.11, $p<0.001$), indicating increased uteroplacental vascular resistance. Similarly, the umbilical artery PI was elevated in the DILI group (1.18 ± 0.24 vs 0.89 ± 0.15, $p<0.001$), reflecting impaired fetoplacental blood flow.

In contrast, the middle cerebral artery PI was significantly reduced in the DILI group (1.36 ± 0.22 vs 1.62 ± 0.21, $p<0.001$), consistent with the “brain-sparing” effect. This was further supported by a significantly lower cerebroplacental ratio (CPR) in the DILI group (1.08 ± 0.24 vs 1.71 ± 0.29, $p<0.001$).

The frequency of pathological Doppler findings was markedly higher among patients with DILI. Blood flow impairment was observed in 61 (62.2%) cases compared to 5 (12.5%) in the control group ($p<0.001$). A CPR value below 1.08 was detected in 36 (36.7%) patients in the DILI group versus 2 (5.0%) controls ($p<0.001$).

Table 3.

Doppler parameters and placental insufficiency

Indicator	Main group, n=98	Control group, n=40	P
Uterine artery PI	0.92 ± 0.16	0.71 ± 0.11	<0.001
Umbilical artery PI	1.18 ± 0.24	0.89 ± 0.15	<0.001
Middle cerebral artery PI	1.36 ± 0.22	1.62 ± 0.21	<0.001
Cerebroplacental ratio (CPR)	1.08 ± 0.24	1.71 ± 0.29	<0.001

Indicator	Main group, n=98	Control group, n=40	P
Blood flow impairment, n (%)	61 (62.2%)	5 (12.5%)	<0.001
CPR <1.08, n (%)	36 (36.7%)	2 (5.0%)	<0.001
Fetal growth restriction, n (%)	41 (41.8%)	3 (7.5%)	<0.001

Furthermore, fetal growth restriction was significantly more common in the DILI group, affecting 41 (41.8%) pregnancies compared to only 3 (7.5%) in the control group (p<0.001).

Overall, these findings indicate that DILI in pregnancy is strongly associated with increased vascular resistance, redistribution of fetal circulation, and a higher incidence of placental insufficiency and adverse perinatal outcomes.

The odds ratio analysis demonstrated a strong association between DILI and the development of placental insufficiency. Pregnant women with DILI had a significantly higher risk of placental insufficiency compared to the control group (OR=11.54; 95% CI: 4.15–32.07; p<0.001).

In addition, increased placental stiffness (>25 kPa) was identified as an independent risk factor for placental insufficiency. Patients with elevated placental stiffness had a 4.56-fold higher risk of developing placental dysfunction compared to those with lower stiffness values (OR=4.56; 95% CI: 1.80–11.59; p=0.001).

Table 4.

Odds ratio (OR) for placental insufficiency

Factor	Event	No event	OR (95% CI)	p-value
DILI (n=98) vs control (n=40)	61/98 vs 5/40	37/98 vs 35/40	11.54 (4.15–32.07)	<0.001
Placental stiffness >25 kPa	34/42 vs 27/56	8/42 vs 29/56	4.56 (1.80–11.59)	0.001

These findings suggest that both DILI and increased placental stiffness are significant predictors of placental insufficiency and may be useful for early risk stratification in pregnant women.

The presence of DILI was associated with an over 11-fold increased risk of placental insufficiency compared to controls. Furthermore, within the main group, elevated placental stiffness (>25 kPa) demonstrated an independent clinical association with placental insufficiency (OR=4.56; 95% CI: 1.80–11.59).

The relationship between ALT levels and liver stiffness (by stiffness quartiles) demonstrated a clear positive trend. ALT values progressively increased with rising liver stiffness across quartiles, indicating a direct association between hepatic stiffness and the severity of hepatocellular injury.

A clear inverse relationship between placental stiffness and the cerebroplacental ratio (CPR) was observed. As placental stiffness increased across quartiles, CPR values progressively decreased, indicating worsening fetoplacental circulation.

Specifically, CPR declined from 1.62 in the first quartile (Q1, ~17 kPa) to 1.38 in Q2 (~21 kPa), 1.09 in Q3 (~25 kPa), and reached 0.86 in the fourth quartile (Q4, ~29 kPa). This trend reflects a progressive redistribution of fetal circulation, consistent with the development of placental insufficiency.

Notably, CPR values below the clinically significant threshold (CPR <1.08) were predominantly observed in higher quartiles of placental stiffness, supporting the association between increased placental rigidity and fetal hemodynamic compromise.

These findings suggest that placental stiffness assessed by elastography is closely associated with impaired fetoplacental blood flow and may serve as an early non-invasive marker of placental dysfunction.

The obtained data demonstrate that pregnant women with DILI develop a combined impairment of two functionally interconnected systems hepatic and placental. An increase in liver stiffness (LSM)

was associated with enhanced cytolysis and a moderate decrease in hepatic synthetic function, which is consistent with current clinical guidelines on DILI.

In normal pregnancy, the literature indicates that liver stiffness may physiologically increase toward the third trimester. However, in the present cohort, the mean LSM values significantly exceeded those reported for uncomplicated pregnancies. This suggests that LSM can be considered a useful tool for distinguishing pathological from physiological increases in liver stiffness.

Placental elastography studies in preeclampsia, fetal growth restriction (FGR), and other placenta-mediated disorders have demonstrated increased Emean/SWV values and greater tissue heterogeneity. In our study, a similar trend was accompanied by a decrease in CPR and an increased incidence of abnormal blood flow, indicating a pathophysiological link between inflammatory-toxic liver injury, endothelial dysfunction, and impaired placental maturation.

A clinically significant finding was the identification of a high odds ratio for placental insufficiency both in patients with DILI overall and in those with placental stiffness >25 kPa. This supports the inclusion of placental shear-wave elastography (SWE) in the extended monitoring protocol for pregnant women with drug-induced cytolysis.

Conclusion. Pregnant women with drug-induced liver injury exhibit pronounced biochemical signs of cytolysis and impaired hepatic synthetic function. Liver elastography demonstrates a significant increase in LSM compared to physiological pregnancy, while placental elastography reveals elevated Emean, Emax, and increased tissue heterogeneity. Placental insufficiency occurs significantly more frequently in DILI compared to controls; the calculated odds ratio was 11.54 (95% CI: 4.15–32.07). Placental stiffness >25 kPa may be considered a clinically relevant threshold for increased risk of placental insufficiency. The combined use of biochemical markers, Doppler assessment, and liver/placental elastography allows earlier identification of pregnant women at high perinatal risk.

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