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ULTRASOUND AND INTEGRAL DOPPLER MARKERS OF PLACENTAL DYSFUNCTION IN PREGNANT WOMEN WITH CHRONIC HCV INFECTION

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The results of studying ultrasound and Dopplerometric features of the fetoplacental complex in pregnant women with chronic HCV infection are presented and their relationship with biochemical parameters of liver function is evaluated. The study included 69 pregnant women, including 44 patients with chronic HCV infection (the main group), 25 women with a physiological course of pregnancy (the control group). The groups were comparable in age, gestation period, and body mass index ($p > 0.05$). In pregnant women with chronic HCV infection, a statistically significant increase in liver transaminase activity was detected, the thickness of the placenta was significantly less than in the control group ($p = 0.048$), premature maturation of the placenta ($p < 0.001$) was detected. Calcifications and placental cysts were detected more frequently in patients with HCV infection ($p < 0.001$ and $p = 0.054$, respectively). There was an increase in the pulsation index of the uterine arteries and umbilical cord artery in pregnant women with HCV infection ($p < 0.05$); and a decrease in the cerebroplacental ($p = 0.016$) and cerebroplacental-uterine ratios ($p < 0.001$). Comprehensive ultrasound evaluation of the placenta and Dopplerometric examination of blood flow in the mother-placenta-fetus system may be recommended for early detection of placental dysfunction in pregnant women with chronic HCV infection.

Key words: pregnant women, hepatitis C, ultrasound, Dopplerometry, mother-placenta-fetus system.

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УЛЬТРАЗВУКОВІ ТА ІНТЕГРАЛЬНІ ДОПЛЕРОМЕТРИЧНІ МАРКЕРИ ПЛАЦЕНТАРНОЇ ДИСФУНКЦІЇ У ВАГІТНИХ ІЗ ХРОНІЧНОЮ НСВ-ІНФЕКЦІЄЮ

Наведено результати дослідження ультразвукових та доплерометричних особливостей фетоплацентарного комплексу у вагітних із хронічною інфекцією вірусу гепатиту С (НСВ) та оцінено їхній взаємозв'язок із біохімічними показниками функції печінки. До дослідження включено 69 вагітних жінок, з яких 44 пацієнтки з хронічною НСВ-інфекцією (основна група), 25 жінок із фізіологічним перебігом вагітності (контрольна група). Групи були співставними за віком, терміном вагітності та індексом маси тіла ($p > 0,05$). У вагітних із хронічною інфекцією вірусу гепатиту С (НСВ) було виявлено статистично значуще підвищення активності печінкових трансаміназ; товщина плаценти була значно меншою, ніж у контрольній групі ($p = 0,048$); також було виявлено передчасне дозрівання плаценти ($p < 0,001$). Кальцифікати та кісти плаценти частіше виявлялися у пацієнток з НСВ-інфекцією ($p < 0,001$ та $p = 0,054$ відповідно). Відзначено підвищення пульсаційного індексу маткових артерій та артерії пуповини у вагітних з НСВ-інфекцією ($p < 0,05$); а також зниження цереброплацентарного ($p = 0,016$) та цереброплацентарно-маткового співвідношення ($p < 0,001$). Комплексна ультразвукова оцінка плаценти та доплерометричне дослідження кровотоку в системі «мати-плацента-плід» можуть бути рекомендовані для раннього виявлення плацентарної дисфункції у вагітних із хронічною НСВ-інфекцією.

Ключові слова: вагітні, гепатит С, УЗД, доплерометрія, система «мати-плацента-плід».

Hepatitis C virus (HCV) remains one of the leading causes of chronic liver disease worldwide and constitutes a major medico-social problem. Based on estimates by the World Health Organization (WHO), approximately 50 million people are chronically infected with HCV, and more than 1 million new cases are registered annually. In line with the WHO Global Strategy, one of the priority goals is the elimination of hepatitis C as a public health threat by 2030 through a 90% reduction in new infections and a 65 % reduction in mortality [20].

Among women of reproductive age, the prevalence of infection ranges from 0.5 % to 4.8 %, depending on the region, which determines the increasing urgency of the problem of pregnancy management in patients with chronic HCV infection [2].

Although the course of pregnancy in most women with chronic HCV infection remains relatively favorable, accumulated data indicate an increased risk of developing a number of obstetric and perinatal complications. These include preterm

birth, fetal growth restriction, low birth weight, gestational diabetes mellitus, cholestasis of pregnancy, and placental insufficiency. Currently, increasing attention is being paid not only to the risk of vertical transmission of infection, but also to the impact of the chronic inflammatory process on the functional state of the fetoplacental complex [15, 17, 18].

It is known that HCV possesses not only hepatotropism, but also pronounced extrahepatic effects [5, 9]. Persistence of the virus is accompanied by activation of the systemic inflammatory response, increased production of pro-inflammatory cytokines, development of endothelial dysfunction, impairment of microcirculation, and oxidative stress. These mechanisms may disrupt the processes of placentation and remodeling of the spiral arteries, leading to a decrease in uteroplacental perfusion and chronic fetal hypoxia [2, 4, 8].

In recent years, data have emerged indicating the possibility of infection of placental cells with

hepatitis C virus [5]. Experimental studies have demonstrated the ability of HCV to infect trophoblast cells with the development of ultrastructural changes, impairment of cell proliferation processes, and enhancement of local inflammation. It is suggested that these changes may contribute to the development of placental dysfunction and adverse pregnancy outcomes [19].

The placenta is a unique temporary organ that ensures the transport of oxygen and nutrients, removal of metabolic products, immunological protection of the fetus, and synthesis of pregnancy hormones. Even minor structural changes of the placenta can lead to functional impairments of uteroplacental and fetoplacental blood flow, which is reflected in the intrauterine development of the fetus [9].

At present, ultrasound examination in combination with Doppler velocimetry is the main non-invasive method for assessing the state of the fetoplacental complex [13, 16]. The evaluation of placental thickness and maturity grade, the presence of structural changes, as well as quantitative assessment of blood flow in the uterine arteries, umbilical artery, and fetal middle cerebral artery allow timely detection of signs of placental insufficiency and chronic fetal hypoxia. Of particular diagnostic value is the calculation of the cerebroplacental ratio as an integral indicator of redistribution of fetal circulation.

Despite the significant number of studies devoted to chronic HCV infection, ultrasound and Doppler features of the fetoplacental complex in this pathology remain insufficiently studied. Available publications are often limited to the analysis of pregnancy outcomes, whereas the relationship between structural changes of the placenta, disorders of uteroplacental hemodynamics, and the functional state of the liver has been insufficiently studied.

In this regard, comprehensive assessment of ultrasound and Doppler characteristics of the fetoplacental complex in pregnant women with chronic HCV infection is of undoubted scientific and practical interest and may contribute to the improvement of antenatal monitoring of this category of patients.

The purpose of the study was to investigate the ultrasound and Doppler features of the fetoplacental complex in pregnant women with chronic HCV infection and to evaluate their relationship with biochemical parameters of liver function.

Materials and methods. The clinical selection of patients was carried out on the basis of the Republican Clinical Hospital named after Academician Mir-Kasimov. A single-center prospective comparative study was conducted in 2022–2025. The study included 69 pregnant women, of whom 44 patients with chronic HCV infection constituted the main group, and 25 women with physiological course of pregnancy constituted the control group.

Inclusion criteria for the study were: pregnant women with diagnostically established viral hepatitis C; singleton pregnancy; patients who provided written informed consent to participate in the study. Exclusion criteria: pregnant women with other viral diseases; multiple pregnancy. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The diagnosis of chronic HCV infection was established based on the detection of anti-HCV confirmed by PCR (HCV RNA). At the time of the study, pregnant women had a duration of HCV disease of 6 months or more, on average 7.46 ± 1.84 months.

Clinical and anamnestic parameters were taken into account. Body mass index (BMI) was calculated

using the formula: $BMI = \frac{\text{weight (kg)}}{\text{height (m)}^2}$; blood levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined by spectrophotometric method. All participants underwent ultrasound examination and Doppler velocimetry, which were performed in the third trimester (at a gestational age of 30–35 weeks) according to a uniform protocol. During ultrasound examination of the placenta, its location, thickness, structural maturity, and the presence of echogenic inclusions (calcifications, cysts), as well as amniotic fluid were determined. Ultrasound Doppler examination of blood flow in the mother-placenta-fetus system was performed using a GE Voluson S8 scanner (GE Healthcare, USA) with transabdominal probes at frequencies of 3.5 and 5.0 MHz in continuous and pulsed wave Doppler mode. Blood flow scanning of the uterine and middle cerebral arteries, as well as the umbilical artery, was performed. The pulsatility index (PI) was measured; the cerebroplacental ratio was calculated using the

formula: $CPR = \frac{\text{PI of the middle cerebral artery}}{\text{PI of the umbilical artery}}$; and the cerebroplacental-uterine ratio (CPUR) = $\frac{CPR}{\text{mean uterine artery PI}}$.

Statistical analysis of the data was performed using SPSS software (IBM Corp., USA). The normality of distribution of quantitative data was assessed using the Shapiro-Wilk test. For normally distributed data, the results were presented as mean and standard deviation ($M \pm SD$), and comparisons between groups were performed using the two-sample Student's t-test for independent samples. Categorical data was compared using Pearson's χ^2 criterion. The Pearson correlation coefficient is calculated. Statistical estimates were considered significant at a value of $p < 0.05$.

Results of the study. The age of the examined women ranged from 27 to 36 years. By gestational age, the 69 examined women were distributed as follows: 30–31 weeks – 23 (33.3 %) women, 32–33 weeks – 27 (39.1 %), and 34–35 weeks – 19 (27.5 %)

women. The groups were comparable in terms of age, gestational age, and body mass index ($p>0.05$), which

indicates their homogeneity and minimizes the influence of these factors on the study results (Table 1).

Table 1

Clinical and demographic characteristics of the examined pregnant women

Indicator	HCV (n=44)	Control (n=25)	P
Age, years	31.5±2.14	30.84±2.22	0.831
Gestation period, weeks	32.34±1.57	32.4±1.55	0.978
BMI, kg/m ²	24.16±2.74	25.70±2.88	0.70
Primiparous, n (%)	26 (59.1)	17 (68.0)	0.463
Repeat births, n (%)	18 (40.9)	8 (32.0)	
ALT, Units/l	73.16±13.94	26.78±2.44	0.002
AST, Unit/l	57.22±13.51	24.77±1.91	0.020

However, in pregnant women with chronic HCV infection, a statistically significant increase in hepatic transaminase activity was revealed. The obtained results reflect the persisting biochemical

activity of chronic HCV infection during pregnancy. The results of ultrasound examination and Doppler velocimetry are presented in Table 2.

Table 2

Ultrasound and Doppler velocimetric parameters of the fetoplacental complex

Indicator	HCV (n=44)	Control (n=25)	P
Ultrasound indicators			
Thickness of the placenta, mm	27.74±1.60	32.84±1.96	0.048
Degree of maturity of the placenta, n (%)			
1 degree	0	25 (100)	<0.001
2nd degree	16 (36.4)	0	
3rd degree	28 (63.6)	0	<0.001
Calcifications, n (%)	27 (61.4)	2 (8.0)	<0.001
Placental cysts, n (%)	6 (13.6)	0	0.054
AFI, cm	11.89±1.91	14.08±0.26	<0.001
Doppler indicators			
PI of the uterine artery	1.33±0.10	1.04±0.08	0.027
PI of the umbilical artery	1.29±0.13	0.91±0.08	0.015
PI of the middle cerebral artery	1.39±0.23	1.33±0.14	0.824
Integral Doppler parameters			
CPR	1.18±0.23	1.47±0.15	0.016
CPUR	0.97±0.21	1.36±0.22	<0.001

Note: AFI – amniotic fluid index; CPR – cerebroplacental ratio; CPUR – (Cerebroplacental-Uterine Ratio).

In pregnant women with HCV infection, placental thickness was significantly lower than in the control group ($p=0.048$). In addition, the majority of patients in the main group showed premature placental maturation: grade II maturity was diagnosed in 36.4 % of pregnant women and grade III – in 63.6 %, whereas in the control group, grade I maturity was observed in all cases ($p<0.001$). Placental calcifications and cysts were more frequently detected in patients with HCV infection ($p<0.001$ and $p=0.054$, respectively).

The obtained data indicate more pronounced structural changes of the placenta in pregnant women with HCV infection, which may be attributed to persistent chronic inflammation, endothelial dysfunction, and impaired remodeling of placental tissue.

Analysis of Doppler parameters revealed a statistically significant increase in the pulsatility index of the uterine arteries and the umbilical artery in pregnant women with HCV infection compared to the control group ($p<0.05$).

The cerebroplacental ratio in pregnant women with HCV infection was significantly lower

compared to the control group ($p=0.016$). A decrease in the cerebroplacental ratio is considered one of the most sensitive signs of impaired fetoplacental hemodynamics and reflects compensatory redistribution of fetal blood flow in incipient placental insufficiency. A significant decrease in the cerebro-placental-uterine ratio was also observed ($p<0.001$).

Correlation analysis revealed a weak positive correlation between ALT levels and the pulsatility index of the umbilical artery ($r=0.253$, $p>0.05$), as well as a weak negative correlation between ALT levels and the pulsatility index of the middle cerebral artery ($r=-0.166$, $p>0.05$), CPR ($r=-0.246$, $p>0.05$), and CPUR ($r=-0.165$, $p>0.05$). Similar correlations were found for AST: a weak positive correlation with the pulsatility index of the umbilical artery ($r=0.041$, $p>0.05$) and a negative correlation with the pulsatility index of the middle cerebral artery ($r=-0.162$, $p>0.05$), CPR ($r=-0.179$, $p>0.05$), and CPUR ($r=-0.187$, $p>0.05$).

Despite the absence of statistically significant correlations between liver transaminase levels and

parameters of uteroplacental blood flow, the obtained results indicate pronounced structural and functional changes of the fetoplacental complex in pregnant women with HCV infection. Elevated ALT and AST activities reflect ongoing biochemical activity of the disease, whereas the revealed ultrasound changes of the placenta and hemodynamic disturbances may be attributed not only to the cytolytic syndrome but also to the complex effects of chronic inflammation, endothelial dysfunction, oxidative stress, and microcirculatory disorders.

The revealed decrease in placental thickness, high frequency of premature maturation, presence of calcifications, and a tendency toward more frequent detection of placental cysts indicate premature involutive-dystrophic changes of placental tissue. It is known that HCV is capable of infecting trophoblast cells and inducing a local inflammatory response, thereby disrupting angiogenesis and remodeling of the placental vascular bed. These mechanisms are likely to underlie the revealed ultrasound changes.

Discussion. Our data are consistent with the results of studies in which chronic HCV infection was associated with the development of placental insufficiency, fetal growth restriction, and adverse perinatal outcomes [1]. At the same time, most published studies have focused on the analysis of clinical pregnancy outcomes, whereas comprehensive assessment of placental ultrasound characteristics and Doppler parameters has been presented only in a limited number of studies.

Despite the comparability of the study groups in terms of age, gestational age, and BMI, patients in the main group exhibited pronounced ultrasound signs of placental involvement, alterations in uteroplacental hemodynamics, and elevated liver transaminase activity. This suggests that the revealed abnormalities are attributable to chronic HCV infection per se rather than to differences in baseline clinical and demographic characteristics.

In recent years, chronic HCV infection has been regarded not only as a hepatic disease but also as a systemic inflammatory process. Viral replication is accompanied by activation of innate and adaptive immune responses, increased production of proinflammatory cytokines (TNF- α , IL-6, IL-1 β), development of oxidative stress, and endothelial dysfunction. These mechanisms can impair remodeling of the spiral arteries, angiogenesis, and microcirculation in the placenta, leading to the development of chronic placental insufficiency. In addition, data have been published on the possible presence of HCV in placental tissue and infection of trophoblast cells, which further confirms the potential direct effect of the virus on the morphofunctional state of placental tissue [6, 17].

A decrease in the amniotic fluid index in pregnant women with HCV infection was noted. Although marked oligohydramnios was not detected, a significant decrease in AFI compared with the

control group may indicate initial manifestations of chronic placental dysfunction. It is known that the volume of amniotic fluid is closely related to the state of uteroplacental blood flow and placental function; therefore, a decrease in this parameter should be considered in conjunction with other ultrasound signs.

The results of Doppler examination appear equally important. Our study revealed a statistically significant increase in the pulsatility index of the uterine arteries and the umbilical artery, indicating elevated vascular resistance in both the uteroplacental and fetoplacental circulations. Such changes reflect impaired placental perfusion and are considered one of the early functional signs of placental insufficiency.

A decrease in the CPR is of particular interest. Currently, this parameter is recognized as one of the most informative integral Doppler indicators of fetal status. Unlike the assessment of individual vessels, the CPR simultaneously reflects the state of both placental and cerebral blood flow and allows detection of early compensatory fetal responses to chronic hypoxia. The decrease in the cerebroplacental ratio is caused by the combination of increased vascular resistance in the umbilical artery and a relative decrease in resistance in the middle cerebral artery due to the blood flow centralization phenomenon ("brain sparing effect"). Due to this, the CPR is considered a more sensitive indicator of incipient placental insufficiency than individual Doppler indices.

In recent years, an increasing number of studies have demonstrated that a decrease in the CPR is associated not only with fetal growth restriction but also with an increased risk of adverse perinatal outcomes, including intrapartum fetal distress, the need for emergency cesarean section, low Apgar scores, and neonatal admission to the intensive care unit. Even in the absence of pronounced growth restriction, a decrease in the CPR may indicate functional overload of the fetoplacental system [3, 12, 14]. In this regard, the significant decrease in the cerebroplacental ratio we found in pregnant women with chronic HCV infection is of particular clinical interest and suggests the presence of subclinical placental dysfunction.

It should be noted that in our study, the pulsatility index of the middle cerebral artery did not differ significantly between the groups. This likely indicates that at the time of examination, compensatory vasodilation of the fetal cerebral vessels had not yet reached a pronounced degree, whereas disturbances in uteroplacental hemodynamics had already begun to develop. This finding supports current concepts regarding the staged development of placental insufficiency, in which structural changes of the placenta and increased vascular resistance precede the development of pronounced centralization of fetal blood flow.

The revealed decrease in the cerebroplacental-uterine ratio (CPUR) is of particular interest. Unlike the conventional cerebroplacental ratio, the CPUR simultaneously takes into account the state of uterine, placental, and cerebral blood flow, and is therefore regarded as a more sensitive integral indicator of placental dysfunction. In recent years, it has been shown that a decrease in CPUR is associated with a high risk of fetal growth restriction, adverse perinatal outcomes, and the need for preterm delivery [7, 10, 11]. Our data suggest that chronic HCV infection is accompanied by early hemodynamic disturbances in the mother-placenta-fetus system, which can be detected even before the development of pronounced clinical complications of pregnancy.

Despite the revealed changes in ultrasound and Doppler parameters, no statistically significant correlations were found between ALT and AST levels and parameters of fetoplacental blood flow. The absence of a close correlation between the biochemical activity of the disease and the integral parameters of fetoplacental hemodynamics indicates that placental involvement is determined not only by the severity of cytolysis but also by local mechanisms.

Limitations. The limitations of this study include the relatively small sample size and the absence of analysis of neonatal outcomes, which precluded assessment of the prognostic significance of the revealed ultrasound changes.

Conclusion

Pregnant women with chronic HCV infection exhibited pronounced structural changes of the placenta, characterized by a decrease in its thickness, premature maturation, and a higher frequency of calcifications compared to women with a physiologic course of pregnancy. Chronic HCV infection is accompanied by impaired uteroplacental hemodynamics, manifested by an increased pulsatility index of the uterine arteries and the umbilical artery, as well as a decreased cerebroplacental ratio and cerebroplacental-uterine ratio, indicating the development of placental dysfunction.

Only weak, statistically insignificant correlations were found between ALT and AST levels and Doppler parameters, suggesting that the development of fetoplacental complex disturbances is determined by a combination of pathogenetic mechanisms rather than solely by the degree of biochemical activity of the disease.

Comprehensive ultrasound assessment of the placenta and Doppler examination of blood flow in the mother-placenta-fetus system may be recommended for early detection of placental dysfunction in pregnant women with chronic HCV infection and for timely adjustment of obstetric management.

The practical significance of the obtained results lies in the fact that ultrasound examination of the placenta combined with Doppler assessment enables the detection of signs of placental dysfunction in pregnant women with chronic HCV infection even before the development of pronounced clinical complications of pregnancy. This opens up opportunities for more careful dynamic monitoring of this category of patients and timely assessment of fetal status.

Prospects for further research. In the future, it would be promising to conduct larger prospective studies incorporating morphological examination of the placenta, determination of angiogenic factors, markers of endothelial dysfunction, and subsequent assessment of neonatal status. Such a comprehensive approach would allow a more complete understanding of the mechanisms by which chronic HCV infection contributes to the development of placental insufficiency and would facilitate the development of criteria for early prediction of adverse perinatal outcomes.

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