**Functional, hemodynamic and morphostructural changes in the livers of women with preeclampsia and HELLP syndrome**

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Preeclampsia is a multi-factor complication of the second half of pregnancy, the clinical manifestations of which are caused by microcirculatory disorders and hypoxic tissue damage in the target organs, leading to the occurrence of multiple organ failure [1, 2, 3].

The liver, which has a well-defined vascular network is, to a greater or less extent, almost always involved in the pathological process of developing preeclampsia [3, 4]. Progressive hemodynamic disorders in preeclampsia trigger an anaerobic glycolysis process in the liver and lead to the disruption of detoxification, protein synthesis and other critical functions. The morphological indicators of liver damage in severe cases of preeclampsia are focal or periportal necroses of the hepatic tissue, multiple deposits of fibrin deposits in the sinusoidal lumens, impregnation of arteriolar walls, and hemorrhaging.

HELLP syndrome is a variant of severe preeclampsia, with liver failure being a salient feature of the clinical picture, and it is also a variant of thrombotic microangiopathy (TMA), the clinical signs of which are free hemolysis in the serum and urine, increased levels of liver enzymes, and thrombocytopenia [3]. Arterial and capillary thrombosis, which are the underlying causes of the pathogenesis of TMA, leads to fibrin deposition in the hepatic sinusoids, hepatic artery stenosis and, consequently, decreased portal blood flow and ischemic damage to the organ [3, 4]. Thus, serious morphological changes occur in the liver, which lead to impaired liver function and determine the outcome and long-term consequences of HELLP syndrome.

The development of HELLP syndrome against a background of severe preeclampsia is usually considered to be an early stage of maladaptation of the mother’s body in an attempt to meet the needs of the fetus. The particular features of HELLP syndrome are a sub-clinical/atypical clinical picture, as well as rapid progression of the course of the disease. These features, combined with the occurrence of multiple organ failure, constitute the cause of the advent of a “near-miss” condition and a high rate of maternal mortality. Consequently, early preclinical diagnosis of liver damage in pregnant women with preeclampsia is necessary for an objective assessment of the severity of each woman's condition and for choosing rational obstetric tactics. Liver function has been evaluated on the basis of a biochemical study of blood serum in order to determine the level of indicators/markers of cytolytic and cholestatic syndrome, as well as liver cell failure syndrome.

Currently, a comprehensive ultrasound examination of the liver is of great assistance in assessing liver function, in combination with colored Doppler ultrasound scanning, it provides an assessment of the dimensions, structures, and the angioarchitectonics of the organ, as well as of the intra-organ hemodynamics. A Doppler study of hepatic blood flow in pregnant women suffering from preeclampsia is important for various clinical functions, including early detection of liver damage, appropriate assessment of the patient's condition, putting together a multi-disciplinary approach for the management of such patients, and selecting rational obstetric tactics [8, 9]. However, a liver biopsy is still the “gold standard” for detecting the level of liver tissue damage, but this method’s application is limited in obstetric practice due to the technical difficulties involved in performing this procedure at late gestational age, the high risk of complications, as well as the patients’ refusal to have invasive procedures performed on them.

A current trend is to seek new non-invasive tests that are easy to apply and are safe in routine obstetric practice, enabling both functional and structural changes in the organ to be assessed. One of these tests is called the “FibroTest” (by BioPredictive, France). This test is based on determining indirect biochemical markers of liver fibrosis in the blood serum, reflecting the presence and level of morphological changes in liver tissue [9]. In our study, we assessed the possibility of carrying out this method on pregnant women with preeclampsia.

**Research Goal:** To analyze the relationship between functional, hemodynamic, and morphostructural changes in the liver in pregnant women with preeclampsia and HELLP syndrome.

**Materials and methods:**

The maternity ward of the S.S. Yudina City Clinical Hospital formed the base for the study, which was conducted involving 87 pregnant women. Observations were carried out during the term of pregnancy (spanning 28-40 weeks).

The base study group featured patients whose pregnancies were complicated by preeclampsia, including 25 patients with moderate preeclampsia (Sub-group 1), 22 patients with severe preeclampsia (Sub-group 2), and 12 patients with HELLP syndrome that developed during pregnancy (Sub-group 3). The control group featured 30 women who were going through the physiological changes involved in pregnancy. In the main group, patients who had been pregnant before (67%) and who had already gone through childbirth before (52%) were predominant. The average age of the patients in this group was 28.7 ± 6.2 years. Similarly, the control group was dominated by women who were pregnant for the first time (72%). The average age of the patients did not differ significantly from that of the main group and was 26.1 ± 4.2 years (d ≥ 0.05). The socio-economic status of the participants, in both the main group and the control group, was identical. A mandatory criterion for inclusion in the study was granting voluntary informed consent regarding participation in the study. Furthermore, the study's exclusion criteria consisted of the patients having any bad habits (smoking, alcohol consumption, use of narcotics), as well as having pre-existing liver conditions prior to pregnancy.

The clinical and laboratory diagnostics included a blood serum biochemical test to determine the main liver dysfunction markers: ALT, AST, ALP, LDH, total protein, and total bilirubin. Ultrasound scans were carried out using the Voluson S10 ultrasound machine (USA), in B-mode, as per the standard method. We assessed the location, shape, contours and anatomical structure of the liver and gallbladder, the size of the liver, its structure, and the echogenicity of the parenchyma. Doppler color flow mapping mode (DCFM) was used to study the hemodynamic indices in the common hepatic artery, including the diameter, the maximum systolic blood flow (Vm), the end-diastolic blood flow, the Resistive Index (RI), and the systolic/diastolic ratio (SDR). Via sub-costal access, the hepatic artery was viewed where it branches from the celiac trunk so that the angle between the ultrasound probe and the course of the vessel does not exceed 45 degrees. In DCFM mode, the utero-placental and fetal blood flow was assessed by calculating the RI and SDR in the uterine arteries, and the fetal umbilical arteries.

The FibroTest method was applied in order to calculate the level of histological changes in the liver, according to the proprietary algorithm (BioPredictive, France). This was derived through serological markers of liver fibrosis (total bilirubin, haptoglobin, alpha-2-macroglobulin, apolipoprotein A1, gamma-glutamyl transpeptidase) and clinical parameters (height, weight, age, sex), following which the numerical values obtained are converted to the generally recognized METAVIR system, reflecting 4 stages of liver fibrosis (F0 - F4). Venous blood was collected while fasting, and blood serum biochemical analysis was performed in the clinical diagnostic laboratory of the maternity ward at the S.S. Yudina City Clinical Hospital; the FibroTest test was performed in the INVITRO laboratory.

**Study results and discussion**

On the basis of the results of the clinical and laboratory diagnostics of hepatic function in pregnant women with severe preeclampsia and HELLP syndrome, changes were observed in the hepatic samples consistent with hemolysis, cytolytic syndrome, and liver cell failure syndrome. The most pronounced level of these clinical and laboratory syndromes was observed in patients with HELLP syndrome. The results obtained are presented in Table 1.

***Table 1. Clinical and laboratory assessment of liver function in the pregnant women in the study groups***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Indicator | Ref. values | Control GroupM (SD) | Moderate Preeclampsia  | Severe Preeclampsia | HELLP syndrome |
| M (SD) | Deviation | M (SD) | Deviation | M (SD) | Deviation |
| ALT (U/l) | ≤33 | 22.08 (8.09) | 37.31 (13.60) | 0.08 | 149.58 ± (19.70) | <0.0001 | 280.77 (29.41) | <0.0001 |
| ACT (U/l) | ≤33 | 17.59 (9.79) | 21.12 (8.51) | 0.15 | 211.61 (24.49) | <0.0001 | 271.49 (21.85) | <0.0001 |
| ALP (U/l) | 20-130 | 109.51 (17.24) | 129.72 (26.49) | 0.15 | 669.40 (29.34) | <0.0001 | 918.10 (17.73) | <0.0001 |
| LDH (U/l) | 135-214 | 186.23 (22.75) | 221.70 (38.77) | 0.11 | 631.63 (59.22) | <0.0001 | 921.60 (40.37) | <0.0001 |
| Total protein (g/l) | 64-83 | 74.36 (7.23) | 64.70 (7.14) | 0.14 | 59.35 (6.81) | <0.0001 | 45.78  (6.69) | <0.0001 |
| Total bilirubin (mmol/l) | 3-21 | 11.28 (3.16) | 13.71 (3.11) | 0.15 | 28.71  (2.69) | <0.0001 | 77.30  (2.85) | <0.0001 |

During ultrasound examinations of the liver, in both the main group and the control group, the liver size was equal to normal values. Under echography, livers with smooth, clear contours and a fine-grained structure with medium echodensity were observed, which was interpreted as homogeneous and isoechogenic. These results were documented in the women going through the physiological changes involved in pregnancy and also with women suffering from preeclampsia with a moderate level of severity. No dilation of the intrahepatic ducts or changes in the vascular architectonics were observed.

In 23% of the women with severe preeclampsia and 68% of the women with HELLP syndrome, a heterogeneous liver structure and echodensity was noted. The data obtained may explain the morphostructural change in the hepatic tissue caused by hypoxic damage, against a background of microcirculatory disorders. In the Doppler study of the hepatic arterial system in the patients with a physiological course of pregnancy, the mean SDR figure in the hepatic artery amounted to 2.21 ± 0.03, and the RI was 0.55 ± 0.01. Comparatively, a Doppler assessment was conducted of the blood flow in the uterine arteries and the umbilical artery against a background of physiological pregnancy, which amounted to 2.02 ± 0.04, the RI was 0.58 ± 0.01, while the SDR in the umbilical artery was 2.1 ± 0.05, and the RI was 0.45 ± 0.01.

Our study of the blood flow in the hepatic artery and utero-placental vessels in pregnant women with preeclampsia allowed hemodynamic changes typical of this complication to be revealed. Even in cases of moderate preeclampsia with no observable clinical and laboratory manifestations of liver dysfunction, as well as in the absence of echographic signs of changes in the structure of hepatic tissue, a shift in hemodynamic parameters towards increasing peripheral resistance in the hepatic artery was noted. Thus, the average SDR and RI values in the hepatic artery were 3.2 ± 0.07 and 0.66 + 0.01, respectively. The Doppler study of blood flow in the mother-placenta-fetus system also showed a tendency towards increased vascular resistance in the uterine arteries and the umbilical artery. In 8 patients (32%) from this group, stage one blood flow abnormalities were found. The average SDR and RI values amounted to 2.3 ± 0.04 and 0.62 ± 0.01 in the uterine artery, while the values were 2.83 ± 0.04 and 0.49 ± 0.01 in the umbilical artery.

As the level of severity of the preeclampsia increased, there was a progressive worsening of the hemodynamic indicators, in both the arterial system of the liver and in the mother-placenta-fetus system. In severe cases of preeclampsia, an increase in the SDR and RI values was noted in the arteries of the liver up to 3.33 ± 0.09 and 0.71 ± 0.01, in the uterine artery there was an increase of 3.02 ± 008 and 0.68 ± 0.01, and in the umbilical artery there was an increase of 3.39 ± 0.08 and 0.59 ± 0.02, respectively. It should be noted that in 16 patients in this group (72%), impaired blood flow (stage 2) was observed in the mother-placenta-fetus system, and in 6 patients (28%), the blood flow was at a critical level. In comparison, patients with well-developed HELLP syndrome on a background of severe preeclampsia, maximum SDR and RI values were observed in the hepatic artery, amounting to 3.93 ± 0.01 and 0.74 ± 0.02 respectively.

It is noteworthy that the SDR values in the hepatic arteries of the pregnant women with HELLP syndrome were practically two times higher than the average values of the control group, providing proof of massive organ damage affecting the liver tissue and the extreme level of maladaptation of the woman’s body in this complication of preeclampsia. According to the Doppler examination results, 100% of the patients with advanced HELLP syndrome were diagnosed with stage 3 fetal blood flow impairment in the maternal-placenta-fetus system. The results of the Doppler examination in terms of the blood flow in the hepatic artery and in the maternal-placenta-fetus system are presented in Table 2.

***Table 2. Average values for SDR and RI in the in the hepatic, uterine and umbilical arteries***.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indicator** | **Control Group****Av. (**SD**)** | **Moderate Preeclampsia** | **Severe Preeclampsia** | **HELLP Syndrome** |
| **M (**SD**)** | **Dev.** | **M (**SD**)** | **Dev.** | **M (**SD**)** | **Dev.** |
| Umbilical Artery Systolic/Diastolic Ratio | 2.1 (0.3) | 2.83(0.2) | <0.0001 | 3.39 (0.38) | <0.0001 | 3.79 (0.23) | <0.0001 |
| Umbilical Artery RI | 0.45(0.03) | 0.49(0.01) | <0.0001 | 0.59(0.10) | <0.0001 |  0.72 (0.05) | <0.0001 |
| Uterine Artery Systolic/Diastolic Ratio | 2.02 (0.25) | 2.3 (0.21) | <0.0001 | 3.02 (0.38) | <0.0001 | 3.42 (0.45) | <0.0001 |
| Uterine Artery RI | 0.58(0.04) | 0.62(0.02) | <0.0001 | 0.68(0.07) | <0.0001 | 0.75(0.05) | <0.0001 |
| Renal Artery Systolic/Diastolic Ratio | 2.21 (0.17) | 3.2 (0.32) | <0.0001 | 3.33 (0.43) | <0.0001 | 3.93 (0.33) | <0.0001 |
| Renal Artery RI | 0.55(0.02) | 0.66(0.08) | <0.0001 | 0.71(0.01) | <0.0001 | 0.74(0.08) | <0.0001 |
|  |  |  |  |  |  |  |  |

The morphostructural changes in the livers of women with complicated pregnancies and liver function disorders of varying levels of severity were assessed using the FibroTest method. In 10 patients (40%) in the sub-group with moderate preeclampsia, changes were found characteristic of the F1 stage in the METAVIR scoring system, which may indicate initial changes in the hepatic tissue. In the remaining 12 patients (60%) with moderate preeclampsia, the FibroTest result matched the F0 stage on the histological index scale, namely an absence of morphostructural changes in the liver. Thus, even with moderate preeclampsia, there is hypoxic damage and death to hepatocytes, followed by the formation of connective tissue and fibrosis. In patients with severe preeclampsia, we observed more pronounced structural changes in the hepatic tissue. Thus, in 14 patients (60%) with severe preeclampsia, 8 (40%) were identified as being F1 stage, and 8 (40%) as F2 stage according to the METAVIR scoring system.

The greatest morphostructural rearrangement of the hepatic tissue was observed in the sub-group with HELLP syndrome, in which 4 patients (33%) had FibroTest results that fell in the F1 stage, and 6 (50%) fell in the F2 stage. In 2 patients (17%) belonging to this sub-group, widespread fibrosis was detected with multiple porto-central septa being detected without cirrhosis (F3 stage according to the METAVIR scoring system). Thus, all the patients in this sub-group were observed to have experienced organic changes involving varying levels of intensity.

**Discussion of the results**

Our work shows that even in moderate cases of preeclampsia, lowered liver function is observed. As preeclampsia develops, the functional state of the liver progressively deteriorates, until its functioning is reduced to an absolutely minimal level. We believe that the progressive decline in liver function, against a background of increasingly severe preeclampsia, is apparently associated with damage to the organ parenchyma. This is due to microangiopathy and microthrombi formation, which in turn leads to hypoxic damage to hepatocytes and multiple hemorrhages in the hepatic tissue.

Doppler ultrasound assessment of intrahepatic blood flow enabled us to identify characteristic changes in the blood supply to the liver in pregnant women with moderate preeclampsia, even before the appearance of clinical and laboratory signs of liver dysfunction. Decreased hepatic blood flow indicates developing trophic disorders in the hepatic tissue, which should be factored into complex therapy for preeclampsia and when choosing obstetric tactics. Increased vascular resistance in the hepatic arterial basin was observed in parallel with an increase in similar parameters in the uterine and fetal umbilical arteries, pointing to a clear correlation between organ and utero-placental blood flow.

The results we obtained do not contradict the data from a similar study by V.N. Selifonov & M.G. Tukhbatullin (2002). The authors studied how utero-placental and fetal hemodynamics. In addition to blood flow in hepatic vessels, change with gestational age in pregnant women with physiological pregnancy changes and preeclampsia. It was found that with a background of moderate preeclampsia, already from 20-23 weeks of gestation onwards, a significant increase in the vascular resistance index was observed, with this trend persisting and progressing throughout pregnancy. It is apparent there is a direct correlation between the increase in peripheral vascular indicators and the preeclampsia’s level of severity. It was noted that the shift in hemodynamic indices in the hepatic artery, the uterine arteries, and umbilical arteries was mainly due to the diastolic component of blood flow, indicating a hypokinetic type of blood circulation in patients with preeclampsia.

Furthermore, in our study and in the study by V.N. Selifonov & M.G. Tukhbatullin, there was a similar tendency for the SDR and RI to increase in the hepatic artery and the arteries of the mother-placenta-fetus system. Higher recorded values for vascular resistance in the common hepatic artery, umbilical artery, and uterine arteries were associated with severe forms of preeclampsia. It is noteworthy that the Doppler assessment of hepatic blood flow that we carried out allowed us to identify hemodynamic changes in the liver with only a background of moderate preeclampsia, with no deviations in the biochemical parameters of liver function being observed in this group.

The high prognostic value of Doppler assessment of hepatic hemodynamics is referred to in the study by M.V. Ilchenko & N.V. Tukhvatullin (2010), in the course of which high RI and SDR values were detected in the arterial system of the liver and kidneys were regarded as predictors of the development of severe preeclampsia for 11.1 ± 0.7 days before its clinical manifestations appeared. The authors determined the sensitivity and specificity levels of the method as being 88.9% and 90.0% respectively.

The study recently carried out by E.P.Q. Aires *et al.* (2017) also indicates that Doppler assessment of hepatic blood flow in pregnant women with preeclampsia opens up new perspectives in relation to the early diagnosis of preeclampsia. Furthermore, this method, being relatively inexpensive to carry out, is a safe examination method at any gestational age.

Impaired liver function (from moderate to absolute impairment) in severe preeclampsia and HELLP syndrome is accompanied by morphostructural changes in the organ, as confirmed by the results of the FibroTest technique. The results attained doubtless require reconsideration of obstetric tactics for the purpose of an emergency delivery. Recognizing that women with preeclampsia and HELLP syndrome were observed as having pronounced changes in their liver tissue, falling under stages F2 to F3 on the METAVIR scale, such women require dynamic outpatient checks on their liver function in the post-partum period.

Further investigation of the quantitative and qualitative changes in hepatic hemodynamics in patients with preeclampsia is required for the purpose of studying their prognostic potential in relation to assessing the level of severity of preeclampsia and the liver’s level of compensatory capacity, as well as the risk of the preeclampsia becoming full-blown HELLP syndrome.

Thus, the study we conducted demonstrates the advisability of combined liver ultrasound tests, Doppler assessment of intrahepatic blood flow and the FibroTest technique as part of the list of examinations for patients with preeclampsia. This combination of tests, if applied in the early stages of the disease, will enable a more complete and objective assessment of the level and nature of the changes in the liver, the compensatory capacity of the mother’s body, the level of severity of the preeclampsia, and prognosis of its further progression. By determining the quantitative and qualitative characteristics of hepatic blood flow, along with studying the hemodynamic parameters in the mother-placenta-fetal system, we can provide an early highly informative prognostic screening test, in addition to being easily applicable as part of routine obstetric practice.

**Conclusion**

Considering the abovementioned data, early detection of preclinical signs of liver failure in pregnant women with preeclampsia is extremely important. It is beneficial to combine a biochemical assessment of the level of dysfunction with an assessment of hepatic hemodynamics and morphostructural changes in the liver, in order to obtain a more complete picture of the liver condition and the severity of a woman's condition. The results obtained by these assessments should be factored into choosing the obstetric tactics. That is to say, should a minor liver dysfunction arise, it is possible to include hepatoprotector drugs in the complex therapy for preeclampsia, with subsequent dynamic monitoring of organ function with the assistance of a points scale. The progression of liver failure will allow the issue of early delivery to be addressed in a timely manner.

Liver damage in cases of preeclampsia and HELLP syndrome is often not limited to functional changes, rather it is accompanied by structural changes in the organ of varying severity. For a more complete assessment of the extent of liver damage in pregnant women with preeclampsia, using the FibroTest technique is possible. Predictably, there are cases where the pathological processes in the liver that developed in pregnant women against a background of preeclampsia require a long recovery after delivery, due to which, dynamic monitoring for biochemical indicators of liver function is required in the post-partum period. Furthermore, medication for correcting the liver dysfunction may be necessary. Using this may serve as a new means of diagnosis of hepatic insufficiency in pregnant women.

**Source Literature**

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