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The possibility of introducing a normal pregnancy and delivery in patients with established liver cirrhosis

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Abstract

The management of pregnant women with portal hypertension is challenging. In the second trimester, examinations are performed to identify esophageal varices. There are no clear recommendations regarding the primary prevention of bleeding in case of esophageal varices in pregnant women and management in case of bleeding.

There are no recommendations on the preferred mode of delivery (vaginal or caesarean section) for portal hypertension. Since the persistent period is undesirable in the presence of varicose veins, it is recommended, if necessary, to shorten the second stage of labor by applying obstetric forceps or performing vacuum extraction of the fetus. In the presence of obstetric indications, a caesarean section is performed, which is also associated with certain risk; since cirrhosis often has varicose veins of the abdominal wall. In addition there is a tendency to bleed during childbirth, infectious complications, and slow wound healing.

Because of possible medical contraindications and difficulty of prenatal management and delivery of patients with established liver cirrhosis, there are many cases of patients concealing their diagnosis when planning pregnancy and visiting a gynecologist, which, undoubtedly, can lead to concomitant complications and serious consequences that threaten the lives of patients.

The clearest example of the above is the following patient case.

Keywords: Pregnancy; Delivery; Liver cirrhosis, Outcome

1. Introduction

Acute liver failure (ALF) is a rare but potentially fatal complication of pregnancy. The main causes of acute liver failure associated with pregnancy - preeclampsia and HELLP syndrome, acute fatty liver disease (AFL), and intrahepatic cholestasis of pregnancy (ICP) [1, 6, 14] - lead to very severe complications of pregnancy and to high reproductive losses (maternal and perinatal mortality reaches 20-30%). Medical care for patients with acute liver failure should be provided in high-level interdisciplinary medical institutions and requires a multidisciplinary approach [11-14].

Acute fatty liver disease [1, 14] is a rare (occurs with a frequency of 1: 7000 - 1: 16000 pregnancies) and potentially fatal liver damage during pregnancy, the etiology and pathogenesis of which are not fully studied. However, there is no doubt about the connection between the AFL and pregnancy, and the only factor that really affects mortality is prompt delivery. AFL develops mainly during gestational age of 32-36 weeks. Despite the achievements of modern medicine, a high mortality rate (up to 23%) in the case of AFL remains [13].

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Studies have found that liver cirrhosis negatively affects fertility due to metabolic and endocrine disorders. A disorder in hypothalamus-pituitary axis in combination with a disorder of estrogen metabolism leads to anovulation, amenorrhea, and, as a consequence, infertility [1-9, 12]. Pregnancy often ends in spontaneous abortion, premature childbirth, or perinatal fetal death [8]. Besides, it is associated with the risk of decline of liver synthetic function and decompensation of cirrhosis, including the development of ascites, bleeding from varicose veins of the esophagus, and encephalopathy [9, 10-14]. The outcome of pregnancy depends on the severity of cirrhosis, and not on its etiology. In the early 1980s, maternal mortality with cirrhosis reached 10.5% [14]. However, according to later data, it decreased to 1.6%, and the frequency of decompensation was 10% [8].

Bleeding from esophageal varices due to portal hypertension of the veins is the leading cause of maternal mortality in pregnancy associated with cirrhosis [8, 11-13]. Portal hypertension in pregnancy increases and reaches a maximum in the second trimester due to an increase in the volume of circulating blood and direct compression of the inferior vena cava by the uterus of a pregnant woman, which prevents venous return [13]. For pregnant women with a history of esophageal varices, the risk of bleeding during pregnancy is 25%. It reaches its maximum in the second trimester and during childbirth. In half of the cases, bleeding is fatal [11].

In the case of non-cirrhotic portal hypertension (NCPH) the synthetic function of the liver usually remains intact, and fertility is rarely impaired. The incidence of bleeding from esophageal varices in pregnant women with NCPH is the same as in the case of cirrhotic portal hypertension, and according to the largest study, its risk is 35% [7]. However, the prognosis in this group of pregnant women is more favorable and the mortality rate is lower (2-6%), probably due to the preservation of the synthetic liver function [1, 13].

2. Patient: P.K., born in 1983, Gugark village, Lori region, Republik of Armenia.

The patient's medical history is related to her previous pregnancies.

2.1. Clinical history

The first pregnancy was in 2006 and ended in spontaneous miscarriage at an early stage (6 weeks). The alleged cause is cytomegalovirus infection. The second pregnancy was in 2008, the patient gave birth to a healthy girl, but during the pregnancy, preeclampsia developed, and the pregnancy proceeded with high blood pressure in the third trimester, which necessitated a cesarean section. Then the patient decided to conceive again. However, twice in 2012 and 2013 an anembryonic pregnancy was diagnosed at 7 weeks. The last pregnancy in 2014, developed normally but was terminated at 10 weeks for medical reasons as the mother was diagnosed with thrombocytopenia, hepatomegaly, splenomegaly, and portal cirrhosis. The patient's desire to have second child forced the family to go to Russia and turn to new doctors.

2.2. Examination data 15.08.2014

According to the examination at the Academic Medical Center “Zapad”, the patient's general condition was satisfactory, the skin and visible mucous membranes were of usual color. The abdomen was soft, non-tender on palpation. The liver was palpable at the edge of the costal margin, the spleen protruded 7 cm from under the edge of the left costal margin, tight of an elastic consistency.

The blood test indicated thrombocytopenia of 31.000, anemia, the number of leukocytes is slightly below normal, and no changes in the blood test were observed. An extended coagulogram, molecular detection of factors was performed: mutations of FII, FV factors were not detected, the patient was heterozygous for the methylenetetrahydrofolate reductase gene and the fibrinogen gene. Administration of aspirin and folic acid was recommended. CT scan without contrast and examination of the portal vessels were performed.

Preliminary diagnosis: extrahepatic portal hypertension (splenomegaly, thrombocytopenia). Differential diagnosis: lymphoproliferative disease and immune thrombocytopenia. The patient was recommended to consult a hematologist at the Hematological Research Center of the Russian Academy of Medical Sciences, as well as to do CT of the abdominal organs with contrast and CT angiography in order to clarify the diagnosis.

2.3. Examination data 15.08.2014.

According to trephine biopsy data (performed at the Pathological Department of Hematological Research Center of the Russian Academy of Medical Sciences), immune thrombocytopenia, myelodysplastic syndrome, myeloproliferative disease and the lymphoproliferative disease was not detected in morphological data of the bone marrow. After having a consultation in the department of chemotherapy of hematological diseases at the National Hematology Research

Center, and according to the histological and cytological analysis of the bone marrow, there were no signs of any disease of the hematopoietic system. The existing changes in the blood are assessed as secondary (hypersplenism).

2.4. Examination data 26.08.2014.

CT scan of the abdominal cavity

The liver is of normal shape and location, is not enlarged (transverse diameter 18.4x10.2x12.9 cm) with moderate signs of cirrhotic transformation. The contours are clear, bumpy. Some disproportion of the liver: caudate-right lobe ratio is 1 (with a norm of < 0.65). The density of the parenchyma is within the normal range. The structure is diffuse inhomogeneous. Against this background, foci of pathological density were not identified. The intrahepatic bile ducts are not expanded. The tracts are differentiated. Intrahepatic and extrahepatic bile ducts are not dilated.

The bile ducts are not dilated in the region of the gallbladder bed. The gallbladder is of normal size, homogeneous, radiopaque calculi are not observed. The extrahepatic bile ducts are not dilated. The spleen is enlarged up to 16.5x5.8x18.4. Splenic index - 1770 (at a rate of 160 - 440), homogeneous**.** Portal vein - 19 mm, splenic vein - up to 16 mm, has a tortuous course.

Superior mesenteric vein - 14 mm. No contrasting defects of the portal vessels were detected. A recanalized umbilical vein with a diameter of up to 13 mm is determined, splenogastric, splenorenal anastomosis, and pulse wave propagation time (PWP) are visualized. Portocaval anastomoses are determined. The splenic artery is tortuous and dilated. Lymphadenopathy, in non-organ formations at the scan level, were not detected.

Conclusion: CT detected liver cirrhosis, splenomegaly, portal hypertension.

2.5. Examination data 26.08.2014.

Consultation at the Hematological Research Center and the results of CT scan of the abdominal organs with intravenous contrast.

The patient has no evidence of blood disorder and immune thrombocytopenia (based on the data of trephine biopsy), no evidence of thrombosis in the portal vein system, no significant mutations favoring thrombophilia status. CT findings indicate signs of portal hypertension and cirrhotic liver transformation.

The etiology of cirrhosis is unknown: there are no data for viral and toxic damage, all autoimmune markers are negative. The patient was not checked for copper metabolism, Wilson's disease (a probable cause of liver cirrhosis) was not excluded, as well as iron metabolism had also not been studied (iron overload syndrome is an unlikely cause of liver damage and the formation of cirrhosis). Conclusion: cirrhosis of the liver of unspecified etiology, Child-Pugh class A. Portal hypertension: splenomegaly. Currently, serum transaminases are within normal limits, liver function is not impaired. There is no need for symptomatic therapy. It is desirable to perform a transjugular liver biopsy, measure the portal pressure gradient. In the future, the patient is a candidate for liver transplantation.

At present, it is advisable to avoid pregnancy, avoid injuries, it is not desirable to perform intramuscular injections, or lift weights (avoid a sharp increase in pressure in the abdominal cavity). In April 2015, the patient flew to Germany, where she was examined at the University Hospital Frankfurt am Main.

2.6. Examination data 03.03.2015

liver with a clearly gross change in structure, parenchymal texture. Intrahepatic lacunar changes are visualized, in which the connection of the portal vein system with the reopened umbilical vein can be observed (Cruveilhier-Baumgarten Syndrome). No ascites. The spleen is greatly enlarged and difficult to measure. The pancreas is normal. The lymph nodes is not visible. Diffuse bypass circuits with clearly high portal pressure ventrally near the ventral wall. Kidneys with a normal parenchymal border. Liver cirrhosis and portal hypertension.

2.7. Examination data 03/16/2015

The liver is rough, the intrahepatic reopened umbilical vein is visualized, as in the previous study. Lacunar vascular changes in the portal system. The liver is caudally convex, wavy. The kidneys are straight. The spleen is still enlarged, protrudes below the lower edge of the kidney. No ascites. Impression is cirrhosis of the liver with portal hypertension and Cruveilhier -Baumgarten syndrome.

2.8. Laboratory data: examination 03/02/2015 and examination: 03/09/2015

The following results are noteworthy: The level of ceruloplasmin slightly decreased at 17.9 mg / dL (norm 20-60). Serology: Hepatitis B. Hepatitis C, hepatitis E - negative. The urine copper excretion did not increase during the day (59.2 mg/day - the norm is <50).

The patient was diagnosed with portal hypertension. Initially, the presence of a hematological disease was possible. But we also clearly saw, as it had already been described in CT data from Russia, the connection with the opened umbilical vein (Cruveilhier Baumgarten syndrome). Varicose veins of the esophagus were visualized. An extended diagnostic panel was carried out to clarify the cause of liver cirrhosis. An unusual slight decrease of ceruloplasmin was observed. Comprehensive diagnostic tests showed no increase in urine copper excretion even after using penicillamine. Therefore, this diagnosis cannot be made. Anti-smooth muscle antibodies were in fact increased, but immunoglobulin G was invisible. We suggested that the patient undergo liver biopsy to detect inflammatory activity. To determine whether it is caused by autoimmune liver disease. We also offered the patient to check actin antibodies at the next visit.

As the patient refused to have a liver biopsy, the doctors in Germany could not recommended immunosuppressive therapy and suggested that the patient comes for an additional examination in a few months. If necessary, the examination recommended by them (determination of actin antibodies and liver biopsy), of course, can be carried out in her country.

Conclusion: Protein S deficiency can be caused (in the vast majority of cases) by a defect in a heterozygous gene. In addition, it has been shown that protein S decreases in case of liver diseases (together with C-reactive protein; both parameters are also suppressed with Marcumar therapy), temporarily in chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis) with a constant decrease to ≈ 50% of initial values. In general, acute phase reactions due to an increase in the c4b binding protein cause a decrease in the activity of the protein S.

Subsequently the patient tried to get pregnant again and visited a doctor in Armenia. The last pregnancy was registered in 2017, but a risk assessment led to the decision to terminate the pregnancy in the second trimester at the Erebouni Medical Center. Possible complications including the possibility of death were explained to the patient. The attending physician suggests considering other ways of having children (surrogacy, adoption).

The patient did not lose hope to become pregnant and visited another doctor at a different clinic, hiding her entire medical history. A gynecologist from the "Slavmed" medical center oversaw pregnancy, without the collaboration with a hematologist and a hepatologist. At 32 weeks of gestation, the patient contacted her leading gynecologist by phone with complaints of bloating, pain in the abdominal and groin area. The doctor realizing that he is faced with a serious complication of pregnancy, recommended taking nifedipine and contacting another more specialized clinic. The patient understood that only her first gynecologist (who previously pointed out the danger of pregnancy and childbirth in her case) can save her and went to the Erebouni Medical Center. The patient was saved by a cesarean section, but the fetus was already dead.

2.9. Extract from the history of 06/18/2021

2.9.1. Diagnosis at admission

Pregnancy 32-6 / 7 weeks, portal hypertension, hepatosplenomegaly, ascites, liver cirrhosis, dead fetus, impending rupture, DIC. Taking into account the existing obstetric situation, a concilium was called, and it was decided to perform a caesarean section under spinal anesthesia. On 06/12/2021 a cesarean section was performed, a dead female fetus was delivered; weighing 2000.0 g, with height 43 cm. Due to atonic bleeding the operation was expanded to extirpation of the uterus without appendages.

Transfusions of blood components (Platelet concentrate, red blood cell mass, and plasma) were performed intraoperatively. In the immediatepostpartum period, the patient was transferred to the intensive care unit of the Erebuni Medical Center, where she received appropriate antibacterial and transfusion therapy, which was subsequently supplemented in the postpatum department with anticoagulant (Clexane) and antianemic (Sorbifer) therapy for 7 days. The recovery period was ordinary, without complications, the wound healed by primary closure. After the healing of the wound, the patient was discharged in a satisfactory condition.

On the 10th day after the cesarean section, at the appointment with a gynecologist, the patient again raised the question of possible motherhood, but this time with the use of in vitro fertilization of a surrogate mother. Currently, the issue of

the feasibility and safety of this procedure and the possible negative effect of stimulating the patient's ovaries, in light of her liver cirrhosis, is being discussed.

3. Conclusion

The paper presents the difficulties faced by a practicing physician who cares for pregnant women who hide anamnestic information which can result in an unfavorable outcome and even death. In addition, the possibility of normal management of pregnancy and delivery in liver cirrhosis is analyzed.

Compliance with ethical standards

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Disclosure of conflict of interest

N. Ghukasyan had the original idea for the work, supervised the project, and wrote the paper. All authors contributed to preparing a draft of the manuscript and have agreed to the final content.

Statement of informed consent

Written informed consent for publication of their clinical details was obtained from the patient.

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