Review

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Rare Types of Spontaneous Liver Ruptures During Pregnancy

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ABSTRACT This literature review is devoted to the problem of spontaneous liver ruptures in pregnant women. Its goal was to raise awareness among physicians as one of the methods to improve the early diagnosis of the disease, as well as to consider the role of the hepatological surgeon in the surgical treatment of rare obstetric diseases. The main links of the pathogenesis of liver ruptures were considered, the problem of high maternal and perinatal mortality was disclosed. Based on the literature data, the most optimal obstetric and surgical treatment and diagnostic tactics for managing pregnant women with spontaneous liver ruptures were determined.

Keywords: spontaneous liver rupture, pregnancy, HELLP syndrome, diagnosis, treatment

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DIC — disseminated intravascular coagulation
MRI — magnetic resonance imaging
MSCT — multislice computed tomography

Liver rupture is a life-threatening condition, accompanied by a severe complex of metabolic disorders, the development of systemic complications: hemorrhagic shock, acute liver failure, disseminated intravascular coagulation syndrome (DIC) and more. According to various data, the frequency of liver damage is from 20 to 47% of all abdominal injuries and does not tend to decrease [1, 2]. Of these, 42.6% are closed liver injuries and 57.4% are open ones [3].

In addition to traumatic injuries, an important problem is the so-called atraumatic (spontaneous) rupture of the liver. The absence of an obvious mechanism of injury, along with nonspecific symptoms, leads to late diagnosis of the disease, which in turn worsens the prognosis of treatment. The causes of spontaneous liver rupture include: liver tumors (hepatocellular carcinoma, hemangioma, adenoma, liver metastases, focal

nodular hyperplasia), liver cirrhosis, amyloidosis, complications of infectious diseases (malaria, syphilis, amoebiasis), etc. [4, 5].

A special group of patients are pregnant women and parturient women, whose liver rupture in most cases is associated with preeclampsia, eclampsia, and *HELLP* syndrome [4]. According to the literature, the level of maternal mortality in spontaneous liver ruptures ranges from 7.5–17%, perinatal mortality is 28–44%, which confirms the high medical and social significance of the problem [6–8].

Today, there is no standard protocol for the treatment of this category of patients; this fact necessitates the consideration of various diagnostic and treatment approaches in the context of saving the life of the mother and child.

In 1844, *Abercrombie J.* first described a case of spontaneous liver rupture, linking its development with pregnancy [9]. Since then, slightly more than 200 such observations have been described in the medical literature, which, apparently, does not correspond to their real clinical occurrence. So, according to *Ghorbanpour M. et al*. one case of spontaneous liver rupture occurs in 40,000–250,000 births, *Vera E. et al.* report a higher incidence of this pathology, which is one case per 30,863 births [10, 11].

With the greatest frequency, the disease occurs in multiparous women after 32 weeks of pregnancy, including the first 15 hours after childbirth. The average age of the patients is about 32.6 years [12]. The trauma of the right lobe of the liver is observed in 75% of cases, of the left lobe in 11% of cases, and in 14% there is bilobar liver lesion [13]. It should be noted that in 85% of cases, the occurrence of non-traumatic liver rupture occurs in the prenatal period of pregnancy, and in 15% — in the postpartum period [14].

In most cases, non-traumatic liver rupture occurs against the background of preeclampsia/eclampsia/*HELLP* syndrome, the incidence of the disease in this group is from 0.05 to 2% [15,16]. In a review *by Dubey S. et al.*, including 93 observations with spontaneous liver rupture, it was noted that 75% of them were diagnosed with *HELLP* syndrome (70/93), 5 women in this group had eclampsia. Severe preeclampsia was noted in 20% of pregnant women (19/93), two of them subsequently had eclampsia. Three patients (3.2%) out of 93 had chronic arterial hypertension with superimposed symptoms of preeclampsia, one patient had isolated proteinuria [8].

The etiology of spontaneous liver rupture associated with *HELLP* syndrome is unknown, however, the main links of pathogenesis are well understood. As a result of heterodimerization of *ATI* receptors with bradykinin *B*2 receptors, the concentration of circulating vasopressors, primarily endothelin and angiotensin II, increases. This process makes them resistant to disintegration by reactive oxygen species, whereby calcium concentration increases, vasospasm occurs and tissue perfusion decreases. Further activation of proinflammatory and procoagulant systems leads to the formation of microthrombosis, ischemia, and necrosis [12].

Rademaker L. singled out the pathophysiological stages of the development of the disease. The first stage, hepatic ischemia, is most likely associated with pre-eclampsia or eclampsia leading to small areas of infarction. The next stage is scarring, tissue remodeling and increased vascularization. Due to poor tissue healing capacity due to persistent intrahepatic hypertension and severe coagulation disorders (in cases associated with the *HELLP* syndrome), multiple microbleeds are induced, eventually leading to a large liver hematoma (stage three). Finally, persistent and growing liver hematoma ruptures Glisson's capsule, causing peritoneal irritation and secondary hypovolemic shock (stage four) [9].

Among other things, the literature describes observations of spontaneous liver ruptures in pregnant women that are not associated with eclampsia or *HELLP* syndrome. *Cimbanassi S. et al.* report a case of liver rupture in a primigravida at 27 weeks of gestation, who was hospitalized for spontaneous hemoperitoneum. The cause of this condition was liver peliosis, a disease that occurs as a result of hyperplasia of the sinusoidal spaces of the liver and is characterized by the presence of multiple hemorrhagic cystic cavities. The authors of the article agree that the development of peliotic hepatitis in pregnant women is associated with a combination of two pathogenetic factors: the use of steroid hormones as part of in vitro fertilization and the presence of antiphospholipid syndrome. Liver peliosis should be considered in light of the differential diagnosis of spontaneous liver rupture in pregnancy when eclampsia, preeclampsia, and *HELLP* syndrome are excluded [13].

Sanford B. et al. report a rupture of a hepatocellular adenoma in a pregnant woman at 31 weeks gestation. The authors point to an increased risk of ruptures larger than 5 cm and recommend active surgical tactics when they are detected [17]. *Doumiri M. et al*. report a case of spontaneous liver rupture in a pregnant woman against the background of acute fatty liver steatosis [18]. *Han GH et al* . presented a case of idiopathic atraumatic liver rupture [19].

Despite the possible variety of causes of liver ruptures, the predominant part of them develops in the course of preeclampsia, eclampsia or *HELLP* syndrome, as mentioned above. This determines the clinical picture of the disease. With preeclampsia, arterial hypertension, edema, and proteinuria are noted. The addition of generalized tonic-clonic convulsions testifies in favor of the development of eclampsia. *HELLP* syndrome is one of the manifestations of a severe form of eclampsia, for its laboratory confirmation Tennessee criteria are used: aspartate aminotransferase (AST) more than 70 IU/l, platelets less than 100×10^9/l, lactate dehydrogenase (LDH) more than 600 IU/l. Clinically, *HELLP* syndrome can manifest itself in various conditions, such as: placental abruption (9–20%), acute renal failure (7–36%), DIC (5–56%), severe ascites (4–11%), pulmonary edema (3–10%), hematoma and liver rupture (about 2%) [20].

Among the symptoms of liver rupture, there are: pain in the epigastrium/right hypochondrium, uncontrolled increase in blood pressure, headache, nausea, vomiting, vaginal bleeding, hematuria, convulsions. Such a symptom complex, along with the relative rarity of the disease, leads to false diagnoses and incorrect tactics for treating pregnant women.

In a review of 93 clinical cases with liver rupture, 39.7% of cases were not correctly diagnosed before surgery. The absence of labor activity, fetal distress, deterioration of the mother's condition with the development of unstable hemodynamics became indications for caesarean section in 76% of cases [8].

The most common methods of instrumental diagnosis of liver rupture include ultrasound and multislice computed tomography (MSCT) of the abdominal organs. In a review *by Vigil-De Gracia P. et al*. of 180 patients with liver rupture/hematoma, the diagnosis was confirmed by ultrasound in 20.6% of cases, MSCT in 14.4%, and during laparotomy in 31.7% , and in 33.3% of patients, the method of diagnosing the disease was not reported [21].

It should be noted that the ultrasound of the abdominal organs has a high sensitivity (75.0–86.7%) and specificity (88.4–100%) and makes it possible to determine the nature of the organ damage [22]. The ultrasound picture of the hematoma of the liver is represented by a zone of reduced echogenicity with uneven contours, the absence of blood flow in this zone. Undoubtedly, abdominal ultrasonography has the advantage of high availability and can be used as a screening for hematoma/liver rupture.

The sensitivity and specificity of MSCT reaches 100%, but this method has a number of disadvantages: 1 — the risk of radiation exposure to the fetus, and therefore the radiologist and neonatologist must evaluate all the pros and cons of the study; 2 — the complexity of the study against the background of ongoing anti-shock measures [22–24]. A number of authors point to the possibility of using magnetic resonance imaging (MRI) in the diagnosis of liver infarctions [25, 26]. An obvious advantage of MRI compared to MSCT is its radiation safety, but the duration of the study offsets this advantage.

Treatment of pregnant patients with spontaneous liver rupture should be carried out with the involvement of surgeons involved in the treatment of liver injuries, hepatosurgeons of highly specialized centers [27]. When choosing a treatment strategy, two factors must be guided: the hemodynamic index and the integrity of the Glisson capsule.

Many authors agree that in the presence of a subcapsular hematoma, treatment should be non-operative. Therapeutic measures should include: antihypertensive, infusion therapy, transfusion of plasma and (or) blood elements (if indicated), correction of hypocoagulation, dynamic ultrasound monitoring of the hematoma. A number of researchers describe the use of recombinant factor VIIa [12, 28]. However, the potential risk of developing thromboembolic complications, as well as the high price of the drug, make its use limited. *Wicke C. et al*. presented a report of a 10-year retrospective analysis of the treatment of 5 patients with subcapsular hematoma. Three of them were treated conservatively, 2 patients required surgery, and one of them underwent liver transplantation [29]. *Wilson R.H., Marshall B.M.* recommend starting liver surgery with increased pain, peritoneal symptoms, expansion or infection of the hematoma, hemodynamic instability or bleeding [30].

Ionkin D.A. et al. reported a case of draining a tense liver hematoma under ultrasound control in order to prevent its suppuration or rupture [31]. The decision on the delivery of pregnant women with subcapsular hematoma of the liver should be based on the clinical condition of the fetus. With a deterioration in vital signs, an emergency delivery is indicated, regardless of the timing of gestation. Caesarean section is the most optimal method of delivery due to the potentially high risk of liver rupture during vaginal delivery [30]. The continuation of pregnancy can be considered in cases of low gestational age of the fetus with positive dynamics from conservative treatment of the disease with careful daily monitoring of the mother's condition [32].

The tactics of treating patients with rupture of the liver capsule has a number of features. In case of hematoma rupture before delivery, median laparotomy with caesarean section and hemostasis is indicated using a surgical aid adequate to the volume of the lesion.

If the disruption of the liver capsule occurred after childbirth, then today the option of choice is endovascular hemostasis. In 1999, a group of scientists led by Rinehart BK proved the effectiveness of arterial embolization [33]. Despite this, this method has not gained wide popularity and in the period from 2000 to 2010 was used only in 6% of cases in combination with other methods of surgical treatment [34].

Grand'Maison S. et al. described the experience of using transcatheter embolization in 7 patients with spontaneous liver rupture in the postpartum period [34]. At the same time, in 3 cases, interventional treatment was undertaken as a primary intervention. The infection of the hematoma developed in one of the patients, which required hemihepatectomy, and in other case necrosis of the liver lobe with subsequent development of liver failure developed. Four patients underwent embolization after conventional surgery. All patients were discharged. In 2006 *Gyang A.N. et al.*, in 2016 *Gutovich J.M.* demonstrated cases of successful selective hepatic artery embolization [35, 36]. As an embolizing material, gelatin sponges were used, capable of slow resorption in the vessel with subsequent restoration of blood flow.

Despite the obvious success of conservative and minimally invasive management tactics, the traditional surgical approach remains the leading method for treating patients with spontaneous liver ruptures.

With stable hemodynamics, surgical intervention is carried out in the course of intensive care. In case of liver damage in the form of a fissure or small ruptures, preference should be given to argon plasma coagulation or suturing of a liver rupture [37, 38]. With extensive liver damage and the inability to achieve hemostasis by suturing, some authors suggest performing ligation of the hepatic artery. Despite the available experimental data that indicate a high risk of developing liver failure, the described clinical observations prove the opposite. So, back in 1964, a group of American scientists led by Brittain R.S. showed good tolerability of this technique. The authors agreed that a key factor in the development of liver failure is insufficient blood flow in the portal vein system [39].

Araujo A.C. et al. presented a report on 10 observations of the treatment of patients with liver ruptures [40]. Five patients received treatment, hepatic artery ligation, two of them underwent cholecystectomy to prevent gallbladder necrosis. Also, 5 patients underwent omenthepatopexy, in one patient hemostasis was achieved by applying a hemostatic suture. There were no deaths in this sample. Some authors used collagen sponges, synthetic compression meshes, and fibrin gel as an addition to the main surgical treatment for the purpose of hemostasis [16].

Patients with multiple hematomas, ruptures and crushing of the liver tissue are particularly difficult cases. Surgical management of patients in this category has undergone major changes over the past three decades. Historically, in such cases, hemihepatectomy was performed, which led to high maternal mortality, reaching 75% [41]. In 1991, *Smith L.G. et al*. used the method of perihepatic tamponing in patients with liver rupture, reducing the maternal mortality rate 4-fold (up to 18%) [41].

A few years later, in 1993, *Rotondo M.F. et al*. suggested the *"damage control"* strategy [42], which has now become the standard treatment for patients with severe liver rupture. Literally, the name of the concept is translated as " damage control" and includes multi-stage surgical treatment. At the first stage, with the help of gauze napkins, tight plugging of the liver wound and drainage of the abdominal cavity are performed. For temporary hemostasis, as well as the search for a bleeding vessel, it may be useful to use the Pringle maneuver. In order to prevent infectious complications, a laparostomy is formed, as an alternative, single interrupted sutures can be applied to the skin without involving the aponeurosis and fascia. In one case, the use of the *VAC* system with good clinical effect was described [12].

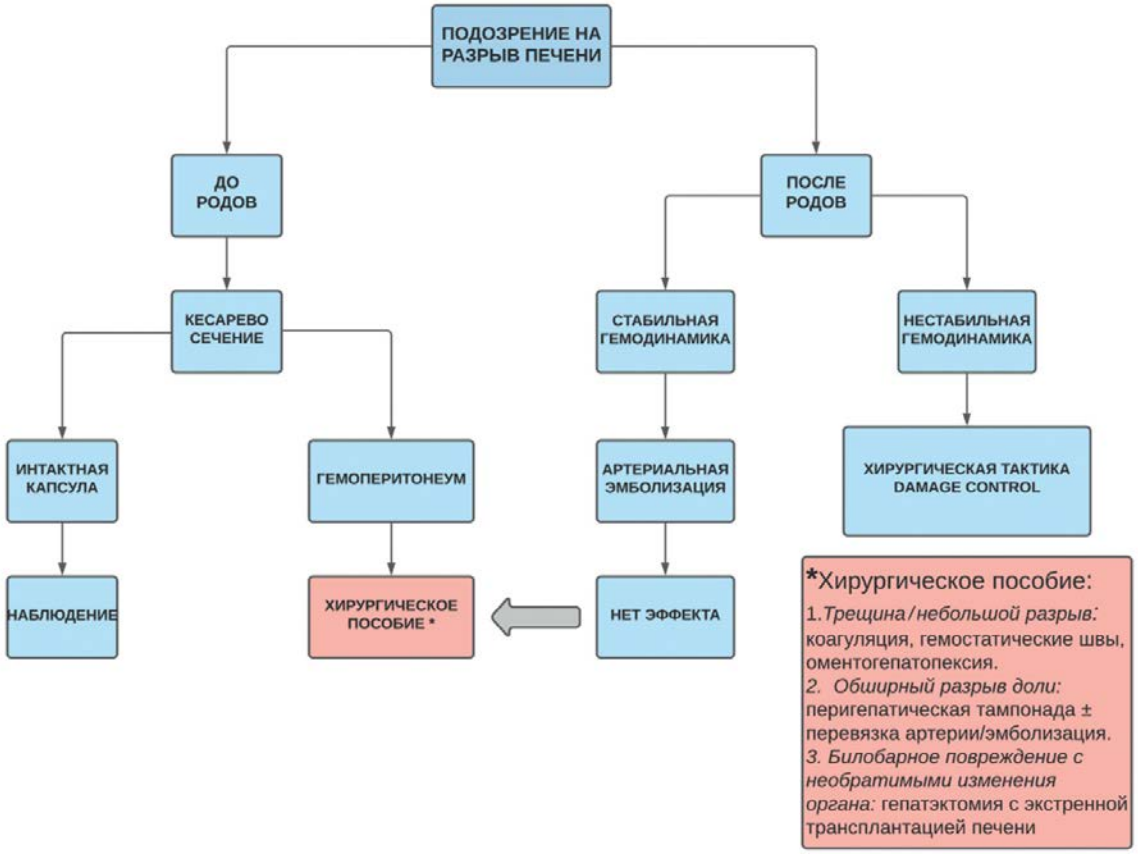
At the next stage, intensive therapy, stabilization of hemodynamics, replenishment of circulating blood volume, elimination of acidosis, coagulopathy, and hypothermia are carried out. After that, they proceed to the next stage of treatment, the final elimination of all damage. According to foreign authors, in 80% of cases, liver tamponade was enough to stop bleeding. Insufficient effectiveness of this technique was noted in patients with arterial bleeding, and therefore, surgical intervention can be supplemented by ligation of the hepatic artery or selective embolization of the vessel.

The greatest difficulty is caused by patients with bilobar rupture of the liver, in which the *"damage control"* tactics is unacceptable due to the non-viability of a large volume of liver tissue. In 1995 *Hunter S.K. et al.* reported the first successful attempt to treat a patient with massive liver damage. As a last resort, she underwent

a hepatectomy with an end-to-side portocaval anastomosis and was placed on the donor liver waiting list. After 13 hours, the patient underwent organ transplantation and was discharged home on the 41st day [43]. Subsequently, until 2010, 12 more such cases were described in the world literature, while all patients remained alive [23].

Spontaneous rupture of the liver of pregnant women is a rare but extremely dangerous pathology that requires immediate coordinated action from doctors of different specialties. Despite the fact that the rate of maternal and perinatal mortality in this pathology has decreased significantly over the past 20 years, the number of adverse outcomes is still high. An analysis of the world literature data showed that the solution to the problem lies in the early diagnosis of the disease and the development of a unified treatment standard.

Based on the data of the literature analysis, the most appropriate, from our point of view, seems to be a surgical approach aimed at achieving hemostasis, taking into account the interests of not only the patient, but also the fetus/newborn (figure).



Treatment tactics for pregnant patients with spontaneous ruptured liver

CONCLUSIONS

1. If *HELLP* syndrome is suspected and patients have complaints of abdominal pain, it is necessary to perform an ultrasound examination of the abdominal organs (screening) to exclude spontaneous hematoma/liver rupture.

2. Identification of spontaneous liver rupture at the prenatal stage is an indication for median laparotomy with caesarean section and achieving hemostasis by suturing the liver rupture. If the disruption of the liver capsule occurred after childbirth, then the option of choice is endovascular hemostasis.

3. In case of extensive liver damage, preference should be given to plugging liver ruptures as part of the *"damage control"* tactic . If the arterial component of bleeding from the hepatic tissue prevails, if it is impossible to achieve hemostasis by stitching, in exceptional cases, ligation of the hepatic artery is acceptable.

4. Massive bilobar injury and non-viability of a large volume of liver tissue are indications for liver transplantation.

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