

Obstetrical Management of Fulminant Viral Hepatitis in Late Pregnancy

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Abstract

Objective: To set up a routine perinatal treatment guideline for fulminant viral hepatitis in late pregnancy (FVHLP).

Method: A summary of literature of successful treatment at various clinical stages. Due to the limited number of prospective studies, retrospective, observational studies and case reports were analyzed and pathophysiological mechanisms were summarized as well.

Results: A comprehensive obstetrical treatment guideline was proposed as follows:

(a) Awareness of FVHLP should be reinforced among medical staff;

(b) Patients diagnosed with FVHLP should be transported to regional expert centers before labor onset;

(c) Supportive medication should be administered to prepare the patients for incoming delivery. A central venous line should be maintained to provide rapid intravenous access and monitor central venous pressure before operation start;

(d) Caesarean section is recommended for the mode of delivery, followed by peripartum hysterectomy to control postpartum hemorrhage;

(e) Peritoneal/abdominal lavage and drainage tube placement are recommended following operation to decrease abdominal pressure and detect post-operational bleeding;

(f) Hypertonic glucose along with insulin topical injection is recommended to promote the healing of wound;

(g) Supportive medication, replenishment of coagulation factors, preventive antibiotics should be given as needed. Adjust the amount and order of intravenous fluid according to the character and amount of drainage and urine.

Conclusion: Vital obstetrical measures taken include supportive treatments, delivery at appropriate time by cesarean section, and prevent and control of various complications. Guidelines developed with more robust research are still needed.

Keywords: Hepatitis; Pregnancy; Obstetrical; Treatment

Introduction

Fulminant hepatic failure (FHF) is defined as the development of hepatic encephalopathy within a short period (generally within 8 weeks) from the onset of original illness [1-3] (Box 1). Although hepatitis viruses B and E are the leading etiologies for fulminant viral hepatitis (FVH) in Asia and Africa [4,5], other viruses, such as herpes simplex virus (HSV), hepatitis virus A and D, parvovirus B19, chickenpox-herpes zoster, transfusion transmitted virus (TTV), and cytomegalo virus (CMV) are not uncommon [6,7]. There are still 15-34% cases whose etiological cause cannot be identified [6,8].

Clinically, fulminant viral hepatitis in late pregnancy (FVHLP) presents with rapid progression and complicated clinical symptoms [8,9]. It also triggers multi-system organ failure (MSOF) which develops rapidly, and may include coagulation disorders, hepatorenal syndrome, hepatic encephalopathy, toxic enteroparalysis, acute lung injury, infection and endotoxemia, and electrolyte disturbances [10,11]. The maternal [4,12] and fetal fatality rate [5] is extremely high (Table 1), ranking FVHLP one of the main indirect causes of maternal and fetal death in developing countries [15,16]. In addition to the complicated pathogenic conditions, two factors leading to failure of rescue should also be noted: the lack of awareness of FVHLP, which would lead to late recognition and incorrect diagnosis (Table 2), and inappropriate obstetrical management. The latter is even more potentially harmful, since it can lead to irreversible progression of a patient's severe condition, or even death. The nature of the disease makes it very difficult to perform a standard controlled clinical

research in treatment, because when rescuing the patients, every effort is made to save their lives, hence there are only a small number of case reports and retrospective analyses available. Based on review of

Country/Area	Virus	Stage of Pregnancy	Fatality Rate (%)
China[5]	HBV/ HEV	Second trimester and beyond	56, 37*
India[13]	HEV	Second trimester	66
		Third trimester	78, 71* [§]
	Non-HEV	Third trimester	54, 46* [§]
Pakistan[14]	HBV/ HEV	Second trimester and beyond	13, 63*
Saudi Arabia[4]	HEV	First trimester	75, 75*
		Second trimester and beyond	54, 49*

*Fetal and neonatal fatality rate
§Rates from acute viral hepatitis

Table 1: Fatality of fulminant hepatitis in pregnancy.

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Received August 22, 2011; **Accepted** January 05, 2012; **Published** January 07, 2012

Citation: Shi Z, Li X, Yang Y, Ma L, Schreiber A (2012) Obstetrical Management of Fulminant Viral Hepatitis in Late Pregnancy. *Reproductive Sys Sexual Disord* 1:102. doi:10.4172/2161-038X.1000102

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Clinical Classification of Fulminant viral Hepatitis

Acute fulminant viral hepatitis

Presents an acute onset with jaundice. Within two weeks, develops into extreme hypodynamia, pronounced gastrointestinal symptoms, hepatic encephalopathy of degree II or above (IV degrees total), prothrombin activity less than 40% without other reasons, liver dullness and progressive shrinking, and progressive deepening of jaundice. Patients with mild jaundice but with other above-mentioned symptoms should be highly suspected.

Subacute fulminant viral hepatitis

Presents an acute onset with jaundice. Between 15 to 24 weeks, develops into extreme hypodynamia, pronounced gastrointestinal symptoms, prothrombin activity less than 40% without other reasons, progressive deepening of jaundice (serum total bilirubin increasing at $>17.1 \mu\text{mol/L/d}$, or $>340 \mu\text{mol/L}$). Subacute fulminant hepatitis which initially presents with hepatic encephalopathy of degree II or above is termed encephalopathy type (including brain edema, hernia, etc.). Cases initially presenting with ascites and related symptoms (including pleural effusion, etc.) are known as ascites type.

Chronic fulminant viral hepatitis

The pathogenesis of chronic fulminant hepatitis includes:

- (1) History of chronic hepatitis or cirrhosis;
- (2) History as a carrier of chronic hepatitis B virus;
- (3) Neither (1) nor (2), but with signs of chronic liver disease (liver palms, arterial spider, etc.). Radiological changes (increased gamma globulin, and decreased or even inverted albumin/globulin ratio);
- (4) Hepatitis confirmed by biopsy;
- (5) Complicated overlapping infection by HBV, HCV, or other hepatitis viruses.

The clinical onset may be the same as subacute fulminant hepatitis, and with the progression of disease, may reach the diagnostic criteria of fulminant viral hepatitis (prothrombin activity less than 40%, and serum total bilirubin $>340 \mu\text{mol/L}$) beyond a course of 24 weeks.

To facilitate determination of treatment efficacy and prognosis, the subacute and chronic fulminant viral hepatitis can be divided into three stages:

Early stage: the basic diagnostic criteria are met, such as extreme hypodynamia, pronounced gastrointestinal symptoms, progressive deepening of jaundice, serum total bilirubin $>340 \mu\text{mol/L}$, prothrombin activity between 30% and 40%, or pathologically confirmed. No obvious encephalopathy, nor ascites are present.

Mid-stage: easily detectable encephalopathy or ascites, bleeding tendency (bleeding or bruising), prothrombin activity between 20% and 30%.

Late stage: Intractable complications, such as hepatorenal syndrome, gastrointestinal bleeding, severe bleeding tendency (at injection sites), severe infection, electrolyte imbalance, or hepatic encephalopathy of degree II and above, cerebral edema, with prothrombin activity less than 20%.

Histopathological Diagnosis

Acute fulminant viral hepatitis

Simultaneous necrosis of liver cells with necrotic area over 2/3 of liver parenchyma, or sub-massive necrosis, or bridging necrosis with severe degeneration of living liver cells. When 50% or more of liver cells remain after the acute phase, liver regeneration can be expected. A poor prognosis may be predicted in case of diffuse microvesicular steatosis.

Subacute fulminant viral hepatitis

Mixed past and present sub-massive necrosis. Mesh fiber collapse in the relatively old necrosis area, with deposition of collagen fibers. Residual liver cell proliferation groups, with large amount of small bile duct hyperplasia and cholestasis.

Chronic fulminant viral hepatitis

With a chronic liver disease (chronic hepatitis or cirrhosis) background, massive (lobular) or sub-massive fresh necrosis of liver cells.

Box 1: Diagnosis of Fulminant Viral Hepatitis [3].

pathophysiological changes and a handful of literature reports, we are discussing the rationale for choice of treatment at different stages, and are proposing a routine obstetrical treatment guideline for FVHLP in the following.

Importance of early recognition and appropriate treatment facilities

Awareness of FVHLP should be reinforced among medical staff to promote early recognition and timely treatment [25]. For pregnant patients with hepatitis, regular perinatal blood tests (aminotransferases and corresponding hepatitis markers are recommended to be monitored weekly since the second trimester) and physical examinations should be emphasized as a priority. Early clinical manifestations of FVHLP include: hypodynamia, decrease in appetite, dark amber urine, deep jaundice, nausea, vomiting, and abdominal distention [26]. Patients diagnosed with or whose symptomology suggests FVHLP should be transported to regional centers expert in its treatment before labor onset to decrease the risk for complications and fatality [27].

A major dilemma: optimal timing of delivery

For patients with FVHLP, pregnancy constitutes a heavy and continuous burden on the liver. On the other hand, labor can potentially trigger the onset of MSOF. Before delivery, most patients' conditions are precarious at best. After stabilizing the patient with supportive medication (may vary from several hours to several days, and include intensive care unit input, replenishment of serum albumin and globulin, restoring coagulation function, reduction of transaminase and toxins, and control of hepatitis virus replication, etc.), the appropriate time for delivery should be determined to relieve the stress of pregnancy on liver. Unfortunately, any bleeding during delivery will significantly tax the liver. Accordingly, medication and supportive treatment must be rigorously maintained throughout delivery and the postpartum period. Optimal indications for delivering the baby include:

- 1) After the patient has been supportively treated and clinical symptoms and signs (including laboratory indices, such as coagulation function, serum albumin, transaminase, total bilirubin, etc.) have been in a steady state for 24 to 48 hours, or

	AVH	FVHLP	AFLP	HELLP	ICP
Characteristic clinical manifestation	Acute self-limiting, and a serum aspartate transaminase elevation of aminotransferases or jaundice or both.[17]	After a typical acute onset, patient become deeply jaundiced and went into hepatic encephalopathy within 4 wk of onset of disease without any past history of chronic liver disease.[18]	Ranging from asymptomatic elevations in aminotransferases to fulminant hepatic failure with jaundice, profound coagulopathy, hepatic coma, and hypoglycemia.[19] Preeclampsia is present in 50% of cases.[20]	Usually with signs of pre-eclampsia and thrombocytopenia[21], 65% patients present with abdominal pain.	Ranging from modest pruritus to intractable itching associated with jaundice.[22]
Liver biopsy	Moderate necrosis	Severe necrosis	Minor necrosis[23], involves a microvesicular fatty infiltrative disorder, hepatic vacuolization and pallor in the central zone	Periportal hemorrhage and fibrin deposition	Bland cholestasis
Jaundice	Moderate to severe	Severe	Mild	Mostly not	Mild to moderate
Serum aminotransferases and coagulation abnormalities	At least fivefold increase of serum aminotransferases	Serum aminotransferases significantly increase at the onset, then decrease as the necrosis of hepatocytes proceed, reduced coagulation abnormalities	The aminotransferases are usually elevated but <1000 U, with longer prothrombin time and low fibrinogen.	Ranging from 70 U to 6,000 U, with 250 U in average.[21]	normal GGTP, elevated aminotransferases (<1000 U)[24], increased serum bile acid level
Viral serologies	Positive	Positive	Not related	Not related	Not related

Abbreviations

AVH: Acute viral hepatitis
 AFLP: Acute fatty liver of pregnancy
 HELLP: Hemolysis, Elevated Liver enzymes and Low Platelet count syndrome.
 ICP: Intrahepatic Cholestasis of Pregnancy
 GGTP: g-glutamyl transpeptidase

Table 2: Differential diagnosis of fulminant hepatitis in late pregnancy (FVHLP).

- 2) Fetal distress is detected and the fetus is viable, or
- 3) After medication treatment yields no improvement in clinical conditions, such as deteriorating of hepatic encephalopathy [28].

Choice of delivery mode

Most FVHLP patients have severe coagulation disorders and hypoproteinemia. When there is trauma in the uterine cavity caused by the detachment of placenta, bleeding is not easily stopped due to shortage of blood coagulation factors and weakened uterine contractions caused by tissue edema, leading to an extremely high risk of postpartum hemorrhage [29], whereas the incision on uterus during cesarean section is much smaller in size, leading to less hemorrhage inside the uterus, and peripartum hysterectomy may be performed when postpartum hemorrhage occurs. Because of preexisting hypovolemia, postpartum hemorrhage would exacerbate liver cell damage. A prolonged vaginal delivery can potentially aggravate the condition by consuming energy and inflicting pain. A previous study has demonstrated that maternal liver function indices deteriorate significantly after vaginal delivery [30]. Recently, due to improved techniques in anesthesia, blood transfusion, anti-infective management and enhanced caesarean section skills among surgeons, risks for negative outcomes and complications in caesarean section deliveries have been reduced. Consequently, researchers and practitioners prefer caesarean section in FVHLP cases [31]. Vaginal delivery is still considered in multiparous patients who have already entered the labor process in which the cervix is mature and delivery is imminent. It has also been shown that fatality rates after caesarean sections are significantly lower than those after vaginal deliveries; among patients whose deaths were attributed to FVHLP, the majority had experienced vaginal deliveries [25,32].

Pre-operative preparation

Before delivery, necessary preparations include extensive monitoring, careful nursing and supportive treatment to ensure stable vital signs and optimize the patient's coagulation function,

serum albumin, transaminase, and total bilirubin levels. Meanwhile, complications should be prevented or promptly treated should any arise. Before a caesarean section, in addition to preparing for blood transfusion, retention of a urinary drainage tube, and newborn resuscitation, it is also crucial to be prepared to

- 1) Perform coloclisis to evacuate colonic content, relieve toxic enteroparalysis and prevent hepatic encephalopathy [10];
- 2) Maintain body temperature during the operation;
- 3) Insert a central venous line to provide rapid intravenous access and monitor central venous pressure. Together with blood pressure and heart rate monitoring, these allow for effective assessment of heart function, preload and blood volume, and help guide the speed and volume of infusing intravenous fluids. For FVHLP patients, central venous cannulation should be performed by experienced doctors to avoid regional hemorrhage, hematoma, hemathorax or hemopneumothorax.

Peripartum subtotal hysterectomy

Peripartum hysterectomy may be performed emergently as a last resort to save the life of a woman with persistent bleeding, or as planned procedure, often in conjunction with cesarean delivery. It is performed in 0.05 to 0.1 percent of all deliveries and 0.5 percent of cesarean deliveries [33]. In the case of FVHLP, due to the already problematic blood clotting function, peripartum hysterectomy is a direct and more effective treatment for a highly probable postpartum hemorrhage or DIC than other medications or conservative treatment such as uterine artery ligation or embolization. A midline vertical abdominal incision should be used, which allows for satisfactory exposure of the operating field, performance of a total hysterectomy if necessary, peritoneal lavage and hand-exploration of the liver while operating. The peripartum subtotal hysterectomy is preferred, which would prevent postpartum hemorrhage and puerperal infection, reduce the development of hepatorenal syndrome and disruption of liver function indices such as bilirubin and transaminase levels. In contrast, in total hysterectomy, it is necessary to deflect the bladder flap significantly downward.

Since there are rich venous plexes along the attachment between the bladder and cervix, deflection of the bladder flap might damage these venous networks and lead to profuse and even uncontrollable bleeding. Coagulation disorders in FVHLP patients make it harder to achieve hemostasis. Moreover, in late pregnancy, cardinal ligaments and uterosacral ligaments are softer and surrounded by regional edema, making it easier to injure the ureters in total hysterectomy. Subtotal hysterectomy reduces the risk for damage and bleeding of the plexus venosus and ureter, and requires less time than a total hysterectomy.

Peritoneal/abdominal lavage and drainage tube placement

Hand-explore the liver to evaluate the size and texture to make a preliminary assessment of prognosis [32,34]. After closing the posterior peritoneal membrane, rinse the abdominal cavity with povidone-iodine for 3-5 minutes, followed by irrigating with a large amount of physiological saline solution (5000 ml) to eliminate bacteria in the abdominal cavity, reduce noxious substances, prevent postoperative infection, and minimize postoperative fever [35]. Place a silica gel drainage tube at the bottom of the pelvic cavity, and sustain it for 3-7 days. The advantages of abdominal drainage are:

- 1) Decreasing abdominal pressure,
- 2) Promoting discharge of harmful substances such as bilirubin,
- 3) Rinsing of abdomen cavity to reduce toxin when necessary,
- 4) Differentiating whether the abdominal distention after operation is caused by bleeding or by ascites. The character and amount of drainage will vary based on the patient's level of hypoproteinemia (leading to ascites) and severity of her coagulation disorder (leading to postoperative bleeding), on which in-time adjustment in medication can be based.

Treatment after delivery

The ascitic fluid collected during caesarean section should be sent for laboratory testing, including biochemical analysis, bacterial culture and drug-sensitivity testing. Hypertonic glucose injection (500g/l) 20 ml along with 8 units of insulin can be subcutaneously injected along the abdominal incision to promote wound healing [36], which is especially helpful for FVHLP patients with hypoproteinemia. Postoperative vaginal irrigation with povidone-iodine reduces the possibility of upward infection from the vagina [37], and also permits observation of vaginal bleeding. Post-operatively, vital signs, central venous pressure, and hourly urine volume should be carefully monitored. Special attention should be paid to changes in laboratory indices, such as water-electrolyte and acid-base balance, liver function, coagulation function, and routine blood counts. As necessary, adjust medication orders, carefully monitoring the volume and intravenous infusion rates. Cleanness of mouth cavity, abdominal incision, abdominal drainage tube, urinary drainage tube, and central venous cannula should be kept. Coagulation factors should be infused to improve coagulation function, as well as albumin to correct hypoproteinemia. Antiviral [38,39], anti-infectives and supportive and symptomatic treatment should be administered as needed through hospitalization, and monitor carefully for complications. Although breastfeeding does not increase the risk of mother-to-child transmission of HBV [40], it is not recommended in FVHLP patients due to their severe clinical conditions.

A proposed routine obstetrical treatment guideline

- (a) Awareness of FVHLP should be reinforced among medical staff;

- (b) Patients diagnosed with FVHLP should be transported to regional expert centers before labor onset;
- (c) Supportive medication should be administered to prepare the patients for incoming delivery. A central venous line should be maintained to provide rapid intravenous access and monitor central venous pressure before operation;
- (d) Caesarean section is recommended for the mode of delivery, followed by peripartum hysterectomy to control postpartum hemorrhage;
- (e) Peritoneal/abdominal lavage and drainage tube placement are recommended following operation to decrease abdominal pressure and detect post-operational bleeding;
- (f) Hypertonic glucose along with insulin topical injection is recommended to promote the healing of wound;
- (g) Supportive medication, replenishment of coagulation factors, preventive antibiotics should be given as needed. Adjust the amount and order of intravenous fluid according to the character and amount of drainage and urine.

Summary

To date, FVHLP has been a challenging problem in both perinatology and hepatology. We discuss and propose a comprehensive treatment guideline for FVHLP based on available literatures and pathophysiological changes. Obstetrical treatments are of vital importance, because a patient's condition may deteriorate rapidly after delivery without proper management. Guidelines developed with more robust research support are still needed.

Conflict of Interest

There was no conflict of interest about this paper. No competing interest declared.

Acknowledgement

The authors thank Dr. Allen Nicholson, Dr. James Bloxton (Temple University), Dr. Patricia Dillon (LaSalle University), Dr. Hao Wang (Department of General Surgery, the Second Affiliated Hospital of Harbin Medical University) and Dr. Joshua Breslau (Princeton University) for their critical review and suggestions.

Funding

The research was supported by Science and Technology Project Foundations of Guangdong Province, China. No. 2005B34201006.

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