

Clinical characteristics of fulminant hepatitis in pregnancy

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Received: 2004-10-19 Accepted: 2004-12-26

Abstract

AIM: To investigate the clinical characteristics of fulminant hepatitis in pregnancy.

METHODS: We compared and analyzed the etiology, clinical characteristics, and laboratory examinations of 25 cases of fulminant hepatitis in pregnancy and 30 cases of fulminant hepatitis not in pregnancy.

RESULTS: HBV infection and chronic fulminant hepatitis were most common both in the pregnant and in the non-pregnant groups. Jaundice, digestive tract symptoms, increase of bilirubin and thrombinogen activity were the main manifestations. The incidence of hepatic encephalopathy (HE) and hepato-renal syndrome (HRS) was significantly different between the two groups. The incidence of preterm labor, dead fetus and neonatal asphyxia was high.

CONCLUSION: Fulminant hepatitis is likely to occur in late pregnancy with more severe complications, which significantly influences maternity, perinatal fetus, and newborn.

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Key words: Pregnancy; Fulminant hepatitis; Clinical characteristics

Li XM, Ma L, Yang YB, Shi ZJ, Zhou SS. Clinical characteristics of fulminant hepatitis in pregnancy. *World J Gastroenterol* 2005; 11(29): 4600-4603

<http://www.wjgnet.com/1007-9327/11/4600.asp>

INTRODUCTION

Fulminant hepatitis (FH) refers to a kind of severe clinical type of hepatitis characterized by acute onset, fast progression, complicated manifestations and poor prognoses. The average mortality rate of FH in our country is over

60%. Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), transfusion transmitted virus (TTV), herpes simplex virus (HSV) and cytomegalo virus (CMV) can all lead to FH, with HBV being the commonest cause (accounting for about 85%). The basic pathologic changes are massive necrosis and degeneration of hepatocytes. The main clinical manifestations are icteric sclera and xanthochromia, hypodynamia and loss of appetite, nausea and vomiting. Bilirubin increases to more than 171 mmol/L, prothrombin time (PT) decreases to less than 40%, progressive shrinkage of liver, significant deterioration of liver function, deviation of enzyme and bilirubin, and inversion of albumin/globulin ratio. The severe complications include hepatic encephalopathy (HE) and hepato-renal syndrome (HRS). The incidence of FH in pregnancy (FHP) is 66 times that of patients not in pregnancy^[1]. The former is more dangerous with a significantly higher incidence of dead fetus, preterm labor and neonatal asphyxia because of interactions of pregnancy and liver disease. It is also among the major causes of maternal and perinatal death and is still left to be solved in the field of liver disease.

We compared 25 cases of FHP and 30 cases of FH not in pregnancy (FHNP) retrospectively to enhance our knowledge about FHP.

MATERIALS AND METHODS

A total of 55 female reproductive-age patients who met the clinical diagnostic criteria approved by Chinese Medical Association (2000, Xi' an)^[2] were admitted in our hospital from January 1993 to February 2004. In the FHP group, there were 25 cases aged from 23 to 37 years, with an average age of 26.7±3.8 years. There were 30 cases in the FHNP group, aged from 18 to 39 years, with an average age of 28.1±5.6 years. There were no significant differences in age distribution ($t = 1.053, P > 0.05$), etiology and clinical classification ($P > 0.05$) between the two groups.

In the improved FHP group, there were eight cases of primipara and three cases of multipara with an average gestational period of 29.8±6.3 wk. Four cases were simple virus infection, four cases had co-infection and three cases had infection of unknown causes. In the death group, there were 10 primipara and 4 cases of multipara with an average gestational period of 30.6±7.0 wk. Nine cases were simple virus infection, one case had co-infection and four cases had infection with unknown causes. There was no significant difference between the two groups in general conditions.

We compared the etiological markers, clinical groups, symptoms and signs, complications, biochemical indices, B-ultrasonography and pregnancy outcomes. The results were analyzed by “*t* test”, “ χ^2 test”, “fidelity rate test” and

Table 1 Laboratory findings of FHP group and FHNP group (mean±SD)

Items	FHP group	FHNP group	<i>t</i>	<i>P</i>
Glutamate-pyruvate transaminase (ALT, U/L)	424.05±285.12	747.04±621.23	1.996	>0.05
Glutamic-oxalacetic transaminase (AST, U/L)	436.92±304.52	534.93±525.73	1.657	>0.05
ALT/AST	0.89±0.96	1.32±1.56	1.201	>0.05
Alkaline phosphatase (ALP, U/L)	199.42±101.02	142.23±50.03	-2.716	<0.05
Total bilirubin (Tbil, µmol/L)	403.11±162.32	460.54±246.45	0.998	>0.05
Direct bilirubin (Dbil, µmol/L)	240.05±111.69	230.44±112.85	-0.316	>0.05
Bile acid (TBA, µmol/L)	105.92±72.17	205.96±37.20	3.053	<0.05
Serum albumin (ALB, g/L)	28.00±4.45	33.49±5.92	3.818	<0.05
Cholesterol (CHOL, mmol/L)	1.70±0.75	1.91±1.00	0.838	>0.05
Cholinephospholipid (CHE, U/L)	3 132.55±983.57	3 885.81±1 510.60	1.490	>0.05
Blood glucose (GLU, mmol/L)	3.03±1.50	5.25±3.82	2.728	<0.05
Blood urea nitrogen (BUN, mmol/L)	9.66±9.07	4.34±4.02	-2.888	<0.05
Creatinine (Cr, mmol/L)	230.99±205.46	60.55±37.47	-4.459	<0.05
Serum calcium (Ca, mmol/L)	2.00±0.24	2.14±0.21	2.100	<0.05
Alpha-fetoprotein (AFP, ng/mL)	186.11±135.74	456.47±1 374.12	0.805	>0.05
Blood ammonia (NH ₃ , µmol/L)	92.05±55.39	127.71±83.30	1.263	>0.05
PT (s)	43.93±43.66	44.10±26.32	0.018	>0.05
PTA (%)	25.33±12.30	20.81±9.44	-1.513	>0.05

“sum of ranks test” through SPSS software. $P < 0.05$ was considered statistically significant.

RESULTS

Etiological markers

The infection rate of HBV was 68% (17/25), HDV 4% (1/25), HEV 24% (6/25) and unidentified type 28% (7/25) in the FHP group. The infection rate of HAV was 3.3% (1/30), HBV 63.3% (19/30), HEV 20% (6/30) and unidentified type 20% (6/30) in the FHNP group. There was no significant difference in etiology between the two groups ($\chi^2 = 3.249$, $P > 0.05$).

Clinical groups

In the FHP group, there were 7 cases of acute FH, 3 cases of sub-acute FH, and 15 cases of chronic FH. In the FHNP group, there were 4 cases of acute FH, 5 cases of sub-acute FH, and 21 cases of chronic FH. There was no significant difference between the two groups ($\chi^2 = 1.879$, $P > 0.05$).

Hepatitis history

Seven cases had hepatitis history in the FHP group and four died. While 17 cases had hepatitis history in the FHNP group and 8 died. There was a significant difference in hepatitis history between the two groups ($\chi^2 = 4.556$, $P < 0.05$).

Clinical manifestations

The main clinical manifestations of FHP were icteric sclera and xanthochromia (100%), yellow urine (100%), hypodynamia and loss of appetite (96%), nausea and vomiting (64%), abnormal behavior (44%), edema of lower limbs (40%), fever, abdominal pain, oliguria (24%), abdominal distention (16%), tarry stools (12%), skin pruritus, gingival bleeding, and loss of weight.

We compared the clinical symptoms of the two groups and found no significant differences except for abdominal distention ($P > 0.05$).

Laboratory findings

Between the two groups, there were significant differences in such indices as alkaline phosphatase (ALP), bile acid (TBA), serum albumin (ALB), blood urea nitrogen (BUN), creatinine (Cr), blood glucose (GLU) and serum calcium (Ca, $P < 0.05$). In the FHP group, ALP, BUN, Cr were higher while TBA, ALB, GLU, and Ca were lower (Table 1).

B-ultrasonography

In the FHP group, 1 case had liver enlargement, 9 cases liver shrinkage, 15 cases spleen enlargement, 15 cases ascites, and 3 cases had no B-ultrasonography results. In the FHNP group, 2 cases had liver enlargement, 6 cases liver shrinkage, 18 cases spleen enlargement, 16 cases ascites, and 2 cases had no B-ultrasonography results. There were no significant differences in B-ultrasonography results between the two groups (χ^2 liver = 1.190, χ^2 spleen = 0.000, χ^2 ascites = 0.246, $P > 0.05$).

Complications

The most common complication was HE (76%). Others were HRS (64%), peritonitis (56%), hemorrhage (56%), and pulmonary infection (16%). Compared to the FHNP group, there were significant differences in the incidence rates of HE, HRS and hemorrhage ($P < 0.05$). Complications were more likely to develop in the FHP group (Table 2).

Table 2 Comparison of complications between FHP group and FHNP group

Complications	FHP (<i>n</i> = 25, %)	FHNP (<i>n</i> = 30, %)	χ^2	<i>P</i>
Peritonitis	14 (56)	13 (43.3)	0.875	>0.05
HE	19 (76)	15 (50.0)	3.905	<0.05
HRS	16 (64)	4 (13.3)	15.128	<0.01
Hemorrhage	14 (56)	1 (3.3)	13.221	<0.01
Pulmonary infection	4 (16)	4 (13.3)	0.000	>0.05
DIC	6 (24)	0 (0)	5.801	<0.05

Gestational period of FHP onset and pregnancy outcome

Onset of FHP in 25 cases was all in middle (28%, 7/25) or late pregnancy (72%, 18/25).

Two cases had spontaneous abortion, five cases dead fetus, six cases preterm labor, seven cases term labor, and four cases had no labor in our hospital. One patient died before labor. The incidence rate of preterm labor and neonatal asphyxia was 33.3% (6/18) and 27.7% (5/18), respectively.

DISCUSSION

HBV infection is the most common cause of both FHP and FHNP, because China is an area with a high incidence of HBV infection^[4,5]. It was reported in national epidemiologic survey from 1992 to 1995 that 9.57% of Chinese are hepatitis B surface antigen positive^[4]. While the carrier state of HBV infection may be the underlying cause of chronic liver diseases^[6-8]. Once triggered, massive liver necrosis or FH will occur. In our study, chronic FH was most common both in FHP group (60%, 15/25) and in FHNP (70%, 21/30). During pregnancy, the vigorous metabolism puts heavy burden on liver and makes it hard to recover^[9,10]. Infection with HBV during pregnancy is more likely to lead to FH with a fast progression.

The onset of FHP is more rapid, which can develop during the whole pregnancy, and most common during late pregnancy^[11] due to heavy burden in late pregnancy^[12]. Because of the interaction between pregnancy and hepatitis, severe immune response and damage caused by multi-factors, a large number of liver cells will undergo necrosis in a short period. Therefore, the conditions of FHP can aggravate very quickly and complications are more likely to develop^[13]. In our study, the main clinical manifestations were as follows: extreme hypodynamia, digestive tract symptoms such as loss of appetite and frequent vomiting, yellow urine, icteric sclera and xanthochromia, liver shrinkage, hepatic odour and early stage of ascites. Whereas abdominal distention was rare, which may be due to the insensitiveness caused by enlarged uterus, HE was most common. The incidence of other complications, such as hemorrhage^[14,15] and HRS^[16] was significantly higher in the FHP group^[17-20], and influenced the prognoses of FHP^[21,22], especially postpartum hemorrhage and disseminated intravascular coagulation (DIC)^[21,23-25], suggesting that postpartum hemorrhage and DIC are common death causes of FHP.

Bilirubin rose, PT prolonged, prothrombin activity (PTA) decreased, hypoproteinemia occurred, albumin/globulin reversed and cholesterol-enzyme separated. Between FHP and FHNP, there were significant differences in ALP, TBA, ALB, BUN, Cr, GLU, and Ca ($P < 0.05$). Since ALP can be produced not only by liver, but also by placebo, ALP is higher in FHP than in FHNP and returns to normal after labor. During pregnancy, progesterone can suppress smooth muscle to weaken gallbladder contractions and relax bile tract smooth muscle. Evacuation of gall bladder is longer, thus leading to cholestasis. Less TBA is discharged, causing decrease of TBA in blood. During pregnancy, the metabolism is high, serum protein and storage of glucogen reduced, while the blood volume increased. Therefore

hypoproteinemia and hypoglycemia are more notable than in FHNP. The fetus in pregnancy needs calcium for development of bones, causing increase of Ca in maternity, meanwhile, ALB and protein-bound Ca decrease. The incidence of higher BUN and Cr is caused by the development of HRS in FHP.

The main dangers of FHP are fetal malformation, preterm labor, abortion, dead fetus in uterus and stillbirth. The incidence of fetal distress and perinatal death is higher^[26]. In our study, such labor outcomes as dead fetus in uterus (20%, 5/25), preterm labor (33.3%, 6/18) and fetal distress (27.7%, 5/13) were significantly higher in FHP group. In normal pregnancy, the incidence of preterm labor is 5-15% and asphyxia is 3-10%^[11]. In FH, there are metabolic disorders all over the body and insufficient energy generation, blood and oxygen supply through placenta. Accordingly, fetal distress, fetus death in uterus and preterm labor are likely to develop, increasing the rate of perinatal distress and mortality.

In order to decrease maternal and perinatal death rate and increase obstetrical quality, we should recognize FHP comprehensively to the make right diagnosis and treat FHP in its early stage.

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Science Editor Wang XL and Guo SY Language Editor Elsevier HK