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Late gestational liver dysfunction and its impact on pregnancy outcomes

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Summary

Objective: The aim of this study was to investigate the impacts of late gestational liver dysfunction and its impact on pregnancy outcomes. *Materials and Methods:* The patients hospitalized for liver dysfunction in their late pregnancy between 2010-2012 were set as the observation group, and the pregnant women with normal liver function at the same period were randomly selected and set as the control group. The impacts towards the pregnancy outcomes were compared between these two groups and the impacts of different-degree transaminase increasing towards the pregnancy outcome were analyzed. *Results:* The incidence rates of cesarean section, postpartum hemorrhage, fetal distress, premature birth, premature rupture of membranes (PROM) of the observation group and the transaminase-severely-increased group (the severe group) were higher, and the differences were statistically significant ($p < 0.01$ or < 0.05); while only the cesarean rate of the mild and moderate group was significantly different from the control group ($p < 0.01$ or < 0.05). The ratios of intrahepatic cholestasis in pregnancy (ICP), gestational hypertension + HELLP syndrome, acute fatty liver in pregnancy (AFLP) of the severe group were higher than the mild and moderate group, and the differences were statistically significant; the non-alcoholic fatty liver disease (NAFLD) group and the unknown cause group mainly showed a mildly increased transaminase; the distributions of viral hepatitis in pregnancy (VHP), post-viral-hepatitis-B cirrhosis, biliary tract disease, and infected toxic liver dysfunction in different-degree increased transaminase groups had no significant difference. *Conclusions:* Liver dysfunction in later pregnancy, especially with severe transaminase increase, might significantly increase the risk of adverse maternal events. The major causes of severe liver dysfunction in late pregnancy were ICP, gestational hypertensive disorders, and AFLP.

Key words: Late pregnancy; Liver dysfunction; Transaminase; Pregnancy outcome; Perinatal infant.

Introduction

Gestational liver dysfunction occurs when pregnant woman exhibit jaundice or liver dysfunction during their pregnancy [1], which includes two major categories: pregnancy-idiopathic and pregnancy complication-induced liver dysfunction [2], such as intrahepatic cholestasis in pregnancy (ICP), acute fatty liver in pregnancy (AFLP), hyperemesis gravidarum or pregnancy-hypertension-caused liver dysfunctions; the etiology of the second category is not related to the pregnancy, such as viral hepatitis in pregnancy (VHP), cirrhosis, primary liver cancer, drug-induced liver injury, etc [1-3].

The etiology of liver dysfunction in late pregnancy is different from that in early and middle pregnancy. The studies found [3-6] that the common diseases in late pregnancy were VHP, ICP, gestational hypertension and AFLP, etc.; while those in early and middle pregnancy were hyperemesis gravidarum, tocolytic drug-induced liver injury, and others. The previous study of this subject found that the incidence of liver dysfunction in late pregnancy was not increased with the increasing gestational weeks and the most common causes of liver dysfunction in late pregnancy were ICP, gestational hypertension, non-alcoholic fatty liver disease (NAFLD), and VHP. With the increasing incidence of NAFLD, serious concern should be taken.

Certain studies have shown that if liver dysfunction occurs in late pregnancy, it might lead to postpartum hemorrhage, fetal distress, premature birth, and other complications that would endanger the safety of mother and child, while the early diagnosis and treatment could significantly improve the prognosis [1, 7, 8]. The impacts of different causes of liver dysfunction in late pregnancy towards its outcomes were also different [8-13], but the reports assessing the impacts of different-degree liver dysfunctions in late pregnancy on pregnancy outcomes are rare. The present authors performed an analysis of the clinical data of 486 cases of late gestational liver dysfunction that were hospitalized for delivery in the Obstetrics Department of Nantong region in the past three years, and aimed to explore its impact, along with various degrees of increased transaminase, on the outcomes.

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Materials and Methods

General information

A total of 643 cases, who were hospitalized for delivery in the obstetrics department of several hospitals, Nantong region, from January 2010 and December 2012 because of the late pregnancy combined with liver dysfunction, were collected; 486 cases with complete clinical data were analyzed. Meanwhile, a total of 230 women hospitalized for delivery during the same period with normal liver function were randomly selected as the control group. The average age of the observation group was: 26.92 ± 4.42 years old, while that of the control group was: 27.33 ± 4.58 years old; the differences in age, pregnancy, and motherhood times between the two groups were not statistically significant. This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of Nantong MCH Hospital. Written informed consent was obtained from all participants.

Research methods

The relevant clinical data were collected and recorded: maternal age, pregnancy and motherhood times; maternal liver function, kidney function, blood clotting function, maternal serum hepatitis virus markers (HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, anti-HCV, hepatitis A, hepatitis D, and hepatitis E antibodies), viral quantitation (HBV-DNA, HCV-RNA), hepatobiliary and fetal ultrasound results; delivery mode, postpartum hemorrhage, premature birth, abnormal amniotic fluid; cases of perinatal deformity, fetal death, and stillbirths. All the participants were performed with uniform training. The automatic biochemical analyzer was used to measure the blood biochemistry; ELISA was used to detect the serum viral hepatitis A, B, C, Dm, and E markers; HBV-DNA and HCV-RNA were performed the fluorescence quantitative PCR detection. Fatty liver and biliary tract infections were confirmed by ultrasound diagnosis.

The inclusion criteria were the following: abnormal liver function group (the observation group): ALT and (or) AST > 40 U/L; normal liver function group (the control group): ALT, AST were ≤ 40 U/L, total bilirubin, bile acid, and glycocholic acid were normal. The exclusion criteria were the following: twins and multiple pregnancy, placenta previa, pregnancy combined with severe cardiovascular diseases, endocrine diseases, immune system diseases, and metabolic diseases.

Based on the ALT and (or) AST results, 41-80 U/L was set as the mildly increased transaminase group (the mild group); 81-120 U/L was set as the moderately increased transaminase group (the moderate group); ≥121 U/L was set as the severely increased transaminase group (the severe group).

The SPSS11.0 statistical software was used; counting data was performed by the χ^2 test, with a $p < 0.05$ considered statistically significant.

Results

Comparison of cesarean section, postpartum hemorrhage, and perinatal conditions

The incidence rates of cesarean section, postpartum hemorrhage, fetal distress, premature birth, PROM, oligohydramnios, perinatal asphyxia, fetal malformations, fetal death, and large infant of the control group had no statistically significant difference with the overall incidence in the present hospital. The incidence rates of cesarean section, postpartum hemorrhage, fetal distress, premature birth, PROM of the observation group were: 73.66%, 4.32%, 17.07%, 18.52%, and 13.58%, respectively, the χ^2 test revealed the statistically significant difference when compared with the control group ($p < 0.05$ or 0.01); while the incidence rates of oligohydramnios, perinatal asphyxia, fetal malformations, fetal death, and large infant had no statistically significant difference between the two groups ($p > 0.05$, Table 1).

Table 1. — *Comparison of pregnancy outcomes between the two groups.*

	Observation group (n=486)		Control group (n=230)		*p*
	Cases	Incidence rate	Cases	Incidence rate	
Cesarean section	358	73.66%	128	55.65%	< 0.01
Postpartum hemorrhage	21	4.32%	3	1.30%	< 0.05
Fetal distress	83	17.07%	26	11.30%	< 0.05
Premature birth	90	18.52%	28	12.17%	< 0.05
PROM	66	13.58%	16	6.96%	< 0.01
Oligohydramnios	36	7.41%	10	4.35%	> 0.05
Suffocation	5	1.03%	1	0.43%	> 0.05
Fetal malformations	5	1.03%	2	0.87%	> 0.05
Fetal death	7	1.44%	2	0.87%	> 0.05
Large infant	35	7.20%	11	4.78%	> 0.05

The incidence rates of cesarean section, postpartum hemorrhage, fetal distress, premature delivery, and PROM of the severe group were higher than the control group, and the differences were statistically significant ($p < 0.05$ or 0.01), while the incidence of oligohydramnios, perinatal asphyxia, fetal malformations, fetal death, and large infant between the two groups were not statistically significant ($p > 0.05$); the mild and moderate group only exhibited the statistically significant difference in the cesarean section with the control group ($p < 0.05$ or 0.01). The remaining situations had no statistical difference when compared with the control group ($p > 0.05$, Table 2).

Ratios and etiology proportions

According to the classification of different degrees of increased transaminase, the observation group was divided into mild, moderate and severe groups, accounting for 53.09%, 21.61%, and 25.30%, respectively.

The severe group had 123 cases, with the main causes as: 66 cases of ICP, accounting for 53.66%; 17 cases of gestational hypertension + three cases of HELLP syndrome, a total of 20 cases, accounting for 16.26%; 12 cases of VHP, accounting for 9.76%; nine cases of AFLP, accounting for 7.32%, among the observation group, three cases of HELLP syndrome, and nine cases of AFLP all occurred in the severe group.

The NAFLD and unknown reason group mainly exhibited mildly increased transaminase and the proportion in the mild group was higher than the moderate and severe groups; the difference was statistically significant ($p < 0.05$

Table 2. — *Comparison of pregnancy outcomes among different-degrees of increased transaminase groups and the control group.*

	Mild	Moderate	Severe	Control
Cesarean section	176**	71*	111**	128
Postpartum hemorrhage	10	3	8*	3
Fetal distress	44	7	32**	26
Premature birth	41	17	32*	28
PROM	31	13	24**	16
Oligohydramnios	20	5	11	10
Suffocation	1	1	3	1
Fetal malformations	3	2	0	2
Fetal death	4	1	2	2
Large infant	23	3	9	11
Total	258	105	123	230

Compared with the control group, *$p < 0.05$, **$p < 0.01$.

Table 3. — *Causes of varying degrees of elevated transaminase groups.*

	Mild	Moderate	Severe	Total cases
ICP	47	26♦♦	66**	139
Gestational hypertension + HELLP syndrome	17	5♦♦	20**	42
AFLP	0	0♦	9**	9
VHP	16	10	12	38
Post-viral-hepatitis-B cirrhosis	2	1	0	3
Biliary disease	3	1	0	4
Infected toxic liver dysfunction	3	3	0	6
NAFLD	35*	7	8	49
Unknown cause	135**	52♦♦	8	196
Total	258 (53.09%)	105 (21.61%)	123 (25.30%)	486

Comparison between the mild and severe groups, *$p < 0.05$, **$p < 0.01$;
Comparison between the moderate and severe groups, ♦ $p < 0.05$, ♦♦ $p < 0.01$.

or 0.01). The distributions of VHP, post-viral-hepatitis-B cirrhosis, biliary disease, and infected toxic liver dysfunction among the three groups had no significant difference ($p > 0.05$, Table 3).

Situations of maternal and perinatal fetal mortality

Two cases of maternal death occurred in the observation group, and also occurred in the AFLP group: one case had intrauterine fetal death when admitted, although the induction of labor was performed immediately, the disease abruptly exacerbated and rapidly progressed to such multi-organ failures as DIC, liver, kidney, respiratory function and others, and the patient died after the invalid rescue; the other case was hospitalized for PROM of single birth (male), after the cesarean section, the patient exhibited postpartum hemorrhage, combined with significant abnormality of coagulation, DIC, hepatic coma, although she was compensated with the clotting factors, fresh plasma, and blood purification, etc., she still died a few days later due to multi-organ failure.

A total of seven perinatal deaths occurred in the observation group: two cases were the AFLP patients, one case was combined with the severe pre-eclampsia, one case was combined with HELLP syndrome, one case was combined with syphilis, and two cases were combined with fetal malformation.

Discussion

Studies had shown that liver dysfunction in pregnancy could increase maternal complications and might threaten both maternal and fetal lives because of postpartum bleeding, preterm labor, fetal distress, and even intrauterine fetal death [14-16]. The results of this study showed that the incidence rates of cesarean section, postpartum hemorrhage, premature birth, fetal distress, and PROM caused by liver dysfunction in late pregnancy were: 73.66%, 4.32%, 18.52%, 17.07%, and 13.58%, respectively, and were all statistically significantly higher than the control group ($p < 0.05$ or 0.01). Jiang *et al.* [17] studied the impacts of liver dysfunction in late pregnancy towards the outcomes, and also prompted that the incidences of premature birth, fetal distress, cesarean section, and postpartum hemorrhage of the liver dysfunction group were significantly increased; postpartum hemorrhage was considered as the extremely serious complication during the childbirth, and ranked the first reason of maternal mortality in China. This was due to the fact that liver synthesize most coagulation factors; when liver function was impaired severely, the synthesis of clotting factor would be significantly reduced, thus the postpartum hemorrhage would occur [18-20]. In addition, the malabsorption of fat-soluble vitamins might lead to vitamin K deficiency and clotting disorders, which also would increase the risk of postpartum hemorrhage [15]. Therefore, the patients with liver dysfunction in late pregnancy should have their liver function and fetus closely monitored; thus the opportunity to terminate the pregnancy might be grasped in order to avoid the occurrence of maternal and perinatal fetal death.

Serum ALT and AST levels were considered as the major sensitive indicators that could reflect the damages of liver cells. Except for severe hepatitis and liver failure, in general, the higher the ALT and AST levels, the more severe the liver dysfunction. In this paper, based on the level of ALT, the liver dysfunction in late pregnancy was divided into mild, moderate, and severe groups, and compared with the control group, respectively, the results revealed that different-degrees of increased transaminase exhibited different effects on pregnancy outcomes and perinatal fetus: the incidence rates of cesarean section, postpartum hemorrhage, premature birth, fetal distress, and PROM of the severe group were higher than the control group; while the mild and moderate group only exhibited a statistical significance with cesarean section when compared with the control group, indicating that the

severely increased transaminase had significant adverse impacts on maternal and neonatal outcomes; while the mildly to moderately increased transaminase would only increase the rate of cesarean section, and had no other significant effects on pregnancy outcomes. When the liver function was severely impaired, besides postpartum hemorrhage, it would also be easy to lead to placental ischemia and hypoxia, thus resulting in the contamination of amniotic fluid, fetal distress, even fetal death, thereby increasing the perinatal fetal or neonatal mortality [18].

The mildly to moderately increased transaminase had little impact towards the mother and perinatal fetus, and clinically, there was no need to be anxious with this kind of case: the active etiological treatment and liver-protection therapy, as well as the strengthened monitoring, could be sufficient, whereas cases with severely increased transaminase should be timely intervened in order to avoid endangering the lives of mother and child.

When a pregnant woman suffers from severe hepatitis and liver failure, there may be a constantly increased bilirubin; transaminase would decrease, namely the dissociation of serum bilirubin and ALT, suggesting that the necrosis of hepatic cells is severe. Thus some pregnant women that present with severe clinical symptoms while their transaminase level is normal, if they are not in the recovery period of treatment, it might often precipitate to a critical condition and need to be aware of the possibility of severe hepatitis and liver failure. In this study, the observation group had 199 cases that had normal transaminase while the bilirubin was increased, the comprehensive analysis found no case of severe hepatitis.

In this study, the severe group included 123 cases; the main disease causes were: 66 cases of ICP, accounting for 53.66%, 17 cases of gestational hypertension + three cases of HELLP syndrome, accounting for 16.26%, 12 cases of VHP, accounting for 9.76%, and nine cases of AFLP, accounting for 7.32%; Jiang *et al.* [17] reported that among the liver dysfunction in late pregnancy, viral hepatitis accounted for 62.2%, ICP accounted for 23.1%, which is not consistent with this article, which might be due to the fact that the samples in this study were mainly obtained from the Obstetrics Department of General Hospital and Maternal and Child Hospital, rather than confined to the infectious diseases hospital or department, thus the relative proportion of viral hepatitis during pregnancy was not high. In this paper, nine cases were AFLP and presented gastrointestinal symptoms before the liver failure: abdominal discomfort, nausea and vomiting, followed by the severely increased transaminase. The disease abruptly intensified and rapidly progressed to DIC and multi-organ failure, among which there were two cases of maternal death and two cases of fetal death. Compared to other causes, the maternal and perinatal fetal mortalities of this group was the highest, which is consistent with Dwivedi and Runmei [21]. Among the ICP patients, 66 cases were in the severe group, and the ratio was significantly higher than in the mild and moderate groups; the transaminase of ICP patients might generally increase to two- to ten-fold than the normal level, while basically it would not be more than 1,000 U/L; ALT was more sensitive than AST, and might be associated with mildly increased bilirubin [6, 15, 22]. Severe ICP might increase fetal distress, premature birth, PROM, contamination of amniotic fluid, and fetal growth restriction, thus greatly impacting the perinatal fetus [18, 23]. Furthermore, gestational hypertensive disorders and HELLP syndrome would also mainly appear with increased transaminase. Researches [11, 24] found that the pre-eclampsia, eclampsia, and HELLP syndrome could significantly increase the mortality of maternal and perinatal infant, preterm birth rate, and perinatal complication rate; this study had two cases of intrauterine fetal death, indicating the large impacts on the pregnancy outcome. The observation group found no case of severe hepatitis and decompensated cirrhosis, and there was no significant difference in the distribution of VHP, post-viral-hepatitis-B cirrhosis, biliary tract disease, and infected toxic liver dysfunction among the three groups, while the transaminase of the NAFLD and unknown reason liver dysfunction group was mainly mildly increased, consistent with the report [25], and this study found that the two groups had no significant adverse effects on pregnancy outcomes (specified in another article), indicating that in general, the degrees of increased serum transaminase would be roughly parallel with the severities of disease, and exhibited certain warning effects towards the prognosis.

In summary, with clinically common, simple, and sensitive indicators of liver function tests, a significantly increased ALT in late pregnancy could often prompt the combination of severe pregnancy complications, which would endanger both maternal and fetal safety; thus high attention is required, while actively searching for the cause. High-risk pregnant women can therefore be treated in a timely manner with active treatment that could strengthening fetal monitoring and grasp the opportunity to terminate the pregnancy, if required, to avoid the maternal and perinatal adverse events. It has a positive significance in improving the quality of perinatal care.

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