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Short Review

Hepatitis B Virus Infection and Intrahepatic Cholestasis during Pregnancy: Review and Management

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Abstract

Hepatitis B Infection (HBV), one of the major epidemics in China, has an impact on mother-to-child transmission. In addition, a number of existing studies have shown that there is a correlation between HBV infection and pregnancy complications and adverse pregnancy outcomes. Intrahepatic Cholestasis of Pregnancy (ICP) has been found to be associated with HBV in many articles. However, the mechanism of ICP is still not clear, and there is no clear management opinion in clinical practice. Therefore, it is necessary to review the research progress of ICP caused by HBV.

Keywords: Hepatitis B; Intrahepatic cholestasis of pregnancy; Management; Review

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Background

ICP is also named as recurrent jaundice of pregnancy, cholestatic liver disease and jaundice of pregnancy. It is one of the most common liver diseases during pregnancy, which is characterized by otherwise unexplained itching and elevated bile acids or transaminases in the second half of pregnancy [1]. China is one of the main areas where HBV infection is endemic, the prevalence of CHB in people under 60 years of age is 7.2% [2], in women of childbearing age is about 6.7-8% [3,4]. In China, ICP occurred more than 100,000 in hospital deliveries, accounting for 1.2 % [5]. Elevated hormone levels and genetic predisposition during pregnancy are important factors for ICP. However, a number of recent studies have found a higher incidence of adverse pregnancy outcomes in pregnant women infected with HBV [6-14], Among them, HBsAg positive pregnant women have a higher risk of ICP [8,13,14], and second child recurrence rate is higher [15]. Meta analysis showed that, not only is there a higher risk of ICP in pregnant women infected with HBV, but also there is an increased risk of HBV infection in ICP patients [16]. These above findings suggest that HBV is a risk factor for ICP.

Clinical Characteristics of ICP in Pregnant Women Infected with HBV

ICP is a hormonal cholestatic liver disease, the third trimester is characterized by pruritus and elevated serum levels of bile acid aminotransferase. But, it is reversible, patients' symptoms usually resolve spontaneously 2 to 3 weeks after delivery, or occasionally as long as 6 to 8 weeks. ICP tends to occur in older, multiple and twin pregnancies [17]. Laboratory manifestations included an increase in total bile acid levels (>10 mmol/L), a 2-to-10-fold increase in aminotransferase (even up to 1000 uI/L) and elevated glutamyltranspeptidase (one-third of cases). Alkaline phosphatase may also rise, but this is not helpful for diagnosis because it also will elevate during pregnancy due to the placental appear. In addition, hyperbilirubinemia (up to 6mg/dL) was found in nearly a quarter of patients [18]. Compared with those of pregnant women (HBV infection alone or ICP alone), Pregnant women with combined ICP and HBV infection, their maternal ICP and viral infection symptoms were more severe [19]. However, studies on the clinical manifestations of HBV infection with ICP are limited and need more research.

Different etiological characteristics associate with risk of ICP

HBeAg(+) carriers are at higher risk of ICP than HBeAg(-) pregnant women. Studies have shown that in different stages of HBV infection, histological activity and mutations are less in HBeAg(+) immunoclearance periods than in HBeAg(-) ones, which suggest that HBeAg will increase the effect of HBV on bile acid metabolism (through immune response), thereby increasing the risk of ICP [20,21]. However, the effect of HBeAg on ICP has been limited and more research is needed [22-24]. HBV patients with high load of HBVDNA have a strong inflammatory response [25,26]. In addition,

the level of HBVDNA load is an important risk factor to predict the course of severe complications in patients with hepatitis B (especially in immune tolerance period) [25,27]. However, the effect of HBV DNA load on ICP has been limited and more research is needed.

Possible Mechanism of Association between HBV Infection and ICP

Although the exact mechanism of association between HBV infection and ICP is unknown, there are a few possible explanations. HBV is a hepatophilic virus that causes infection by binding to receptors on the surface of liver cells. First, the data suggests that HBV may affect immune cells function through Prostaglandin E2 [28,29]. Studies have shown that HBV infection can change the function of natural killer cells, T cells, granulocyte-derived inhibitory cells and other immune cells, which will cause abnormal liver function and bile acid metabolism [30,31]. Furthermore, other studies have shown that the occurrence of ICP may be related to the mutation of drug-resistant related protein genes (ABCB-1 [32], ABCC-2 [33], ABCB-4 [34,35] and NR1H4 [36] coding sequence).

Above abnormalities, along with hormonal changes during pregnancy (high levels of estrogen and progesterone), may increase the risk of ICP [37]. In addition, it is worth mentioning that the down-regulated functional expression of Sodium Taurocholate Cotransporters (NTCP) may be related to the occurrence of ICP. NTCP has been identified as a functional receptor for HBV. HBV can mediate the invasion and infection of HBV through the specific binding of NTCP, which is related to the mechanism of HBV infection [38-40]. At the same time, NTCP is responsible for the transmembrane transport of sodium and bile acids in liver cells (about 80% of the reuptake of bile acids is assumed by NTCP), which maintains the dynamic balance of bile acids in hepatointestinal circulation [41]. Studies have shown that NTCP deficiency leads to refractory hyperbole academia [42,43], and HBV infection downregulates NTCP expression on liver cell membranes [44].

Management of Pregnant Women with HBV Infection Complicated with ICP

Although ICP is a benign disease for the mother, the combination of ICP with HBV infection not only has a severe impact on the newborn, but also aggravates the mother's ICP and viral infection symptoms [19]. Multiple studies have shown that, not only HBV infection or ICP alone, but also HBV infection combined with ICP ,will increase the incidence of fetal adverse events (such as preterm delivery, meconium staining of amniotic fluid, fetal bradycardia, fetal distress and fetal death) [19,20,45]. The risk of adverse events raised with the increase of bile acid levels (especially >40μmol/L) [17]. Therefore, treatment management aims to reduce clinical symptoms, make maternal biochemistry normal and prevent fetal complications.

Ursodeoxycholic Acid (UDCA) is the prior drug of choice for ICP. UDCA can effectively reduce pruritus, reduce serum total bile acid, normalize liver function test, and bring labor closer to term. UDCA should be given to patients with ICP at a dose of 10-15 mg/kg to improve symptoms; However, Severe cholestasis patients cannot use UDCA alone, rifampicin or choline should be added; Dexamethasone should not be the first-line treatment for obstetric cholestasis; Topical emollients are safe, but their efficacy is not known [46]. Antiviral treatment is necessary. Antiviral therapy can improve the symptoms of chronic HBV infection and reduce the incidence of pregnancy complications. The use of tebivudine, lamivudine and tenofovir during pregnancy is safe [47].

Fetal monitoring is essential in clinical management. Early delivery at 37 weeks is recommended because ICP increases the risk of fetal complications. Pregnant women should be informed of the increased risk of continuing pregnancy, perinatal morbidity, maternal morbidity and the risk of stillbirth. In some cases with severe symptoms and very high bile acid levels (>100), delivery earlier than 37 weeks should be considered after steroid treatment. It is safe for ICP mothers to breastfeed [48].

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article.

Competing Interests

The authors declare that they have no competing interests.

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Author's Contribution

Zhi-Hao Huang, Xu-Guang Guo, Shi Ou-Yang, Ting-Ting Peng, Jun-Chao Qiu, Dong-Dong Yu developed the concept of the review, Mei-Ling Liu, Xin-Yue Huang, Guo-Jun Xu participated in its design and coordination and helped draft the manuscript. Ting-Ting Peng, Zhi-Hao Huang, Sheng-Guang Yan contributed to the interpretation. Shi Ou-Yang, Xu-Guang Guo, Jun-Chao Qiu provided a critical review and substantially revised the manuscript. All authors read and approved the final manuscript.

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