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Review Article

# Navigating Hepatitis B Virus Infection and Intrahepatic Cholestasis During Pregnancy: A Review

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## ABSTRACT

Hepatitis B Virus (HBV) infection represents a significant public health issue in China, particularly concerning the transmission from mother to child. Several studies have indicated a link between HBV infection and complications during pregnancy, as well as negative outcomes for both mothers and infants. Intrahepatic Cholestasis of Pregnancy (ICP) has frequently been noted in connection with HBV in various research articles. Despite this association, the underlying mechanisms of ICP remain unclear, and there is a lack of consensus on management strategies within clinical settings. This underscores the need for a comprehensive review of the current understanding of ICP related to HBV.

**Keywords:** Hepatitis B; Intrahepatic cholestasis of pregnancy.

## INTRODUCTION

Intrahepatic Cholestasis of Pregnancy (ICP), also referred to as recurrent jaundice of pregnancy, cholestatic liver disease, or jaundice during pregnancy, is one of the most prevalent liver disorders encountered during gestation. This condition is characterized by unexplained itching and elevated levels of bile acids or transaminases occurring in the latter half of pregnancy [1]. In China, which has a high endemic rate of Hepatitis B Virus (HBV) infection, approximately 7.2% of individuals under 60 years are affected by chronic HBV (CHB) [2], with prevalence rates among women of childbearing age ranging from 6.7% to 8% [3,4]. In the country, over 100,000 cases of ICP have been reported in hospital deliveries, constituting about 1.2% of total births [5]. Hormonal fluctuations and genetic predispositions during pregnancy are significant contributors to the development of ICP. Recent studies indicate an increased incidence of adverse pregnancy outcomes in women infected with HBV [6-14]. Notably, pregnant women who are HBsAg positive exhibit a higher risk of developing ICP [8,13,14], and the recurrence rate in subsequent pregnancies is elevated [15]. Meta-analyses reveal not only a heightened risk of ICP among pregnant women infected with HBV but also an increased susceptibility to HBV infection in ICP patients [16]. These findings suggest that HBV infection serves as a potential risk factor for the development of ICP.

### Clinical Features of ICP in Pregnant Women with HBV

ICP is classified as a hormonal cholestatic liver condition, typically manifesting in the third trimester with symptoms

such as pruritus and elevated serum bile acid levels. Fortunately, the condition is generally reversible, with symptoms often resolving spontaneously within 2 to 3 weeks after delivery, although some cases may take up to 6 to 8 weeks. ICP is more common in older women, as well as those experiencing multiple pregnancies or carrying twins [17]. Laboratory evaluations typically reveal elevated total bile acid levels (greater than 10 mmol/L), a 2 to 10-fold increase in aminotransferases (sometimes exceeding 1000 uI/L), and raised levels of glutamyl transpeptidase (observed in about one-third of cases). Alkaline phosphatase levels may also increase; however, this elevation is not particularly helpful for diagnosis, as it naturally rises during pregnancy due to placental factors. Hyperbilirubinemia, with levels reaching up to 6 mg/dL, has been reported in nearly 25% of patients [18]. Pregnant women with both ICP and HBV infection tend to experience more severe maternal symptoms compared to those with HBV infection alone or ICP alone [19]. However, further investigation into the clinical manifestations of HBV infection in conjunction with ICP is warranted due to limited existing studies.

### Etiological Factors Linked to ICP Risk

Pregnant women who are HBeAg positive are at a heightened risk for ICP compared to those who are HBeAg negative. Research indicates that histological activity and mutations in different stages of HBV infection are less pronounced during the HBeAg positive immunoclearance period than in HBeAg negative phases, suggesting that HBeAg may amplify the impact of HBV on bile acid metabolism via immune responses, thereby increasing the risk of ICP [20,21]. However, further research is necessary to fully understand the influence of HBeAg on ICP [22-24]. Additionally, patients with high HBV DNA levels exhibit a pronounced inflammatory response [25,26]. The level of HBV DNA is a critical predictor of severe complications in hepatitis B patients, particularly during the immune tolerance phase [25,27], yet the specific effect of HBV DNA load on ICP is still not well understood and requires additional study.

### Potential Mechanisms Linking HBV Infection and ICP

While the precise mechanism connecting HBV infection and ICP remains unclear, several hypotheses exist. HBV, being a hepatotropic virus, initiates infection by binding to receptors on liver cell surfaces. Research suggests that HBV may alter immune cell functions via Prostaglandin E2 [28,29]. Studies indicate that HBV infection can modify the activities of natural killer cells, T cells, granulocyte-derived inhibitory cells, and other immune components, leading to dysfunctional liver activity and disrupted bile acid metabolism [30,31]. Additionally, mutations in genes associated with drug resistance, such as ABCB-1 [32], ABCC-2 [33], ABCB-4 [34,35], and NR1H4 [36], may also contribute to the occurrence of ICP.

These abnormalities, coupled with hormonal fluctuations during pregnancy-specifically elevated estrogen and progesterone levels—may heighten the risk of ICP [37]. Notably, the reduced functional expression of Sodium Taurocholate Cotransporters (NTCP), which serve as functional receptors for HBV, could be relevant to ICP's onset. HBV mediates its invasion and infection of hepatocytes via specific binding to NTCP, a mechanism that underscores HBV infection [38-40]. Simultaneously, NTCP plays a crucial role in the transmembrane transport of sodium and bile acids within liver cells (approximately 80% of bile acid reuptake is attributed to NTCP), which is essential for maintaining the dynamic balance of bile acids in the hepatointestinal circulation [41]. Research has indicated that NTCP deficiency can lead to refractory hyperbole academia [42,43], and HBV infection has been shown to downregulate NTCP expression on liver cell membranes [44].

### Management of Pregnant Women with HBV Infection and ICP

Though ICP is generally considered benign for the mother, its combination with HBV infection can significantly impact newborns and exacerbate maternal symptoms related to both conditions [19]. Various studies have established that the coexistence of HBV infection and ICP leads to a higher incidence of fetal complications (including preterm birth, meconium-stained amniotic fluid, fetal bradycardia, fetal distress, and stillbirth) [19,20,45]. The likelihood of these adverse outcomes increases alongside elevated bile acid levels (notably when exceeding 40 μmol/L) [17]. Consequently, the management strategy aims to alleviate clinical symptoms, normalize maternal biochemistry, and prevent fetal complications.

Ursodeoxycholic Acid (UDCA) is the first-line treatment for ICP, as it effectively reduces pruritus, lowers serum total bile acid levels, normalizes liver function tests, and can help prolong pregnancy to term. For patients with ICP, a dosage of 10-15 mg/kg of UDCA is recommended to enhance symptom relief. However, in cases of severe cholestasis, additional medications such as rifampicin or choline should be considered, as UDCA alone may not suffice. Dexamethasone is not recommended as the first-line treatment for obstetric cholestasis. While topical emollients are safe, their effectiveness remains uncertain [46].

Antiviral treatments are also necessary, as they can alleviate chronic HBV infection symptoms and reduce the risk of complications during pregnancy. Medications such as telbivudine, lamivudine, and tenofovir have been deemed safe for use during pregnancy [47].

Fetal monitoring plays a crucial role in the clinical management of these cases. Early delivery at 37 weeks is advised due to the heightened risk of fetal complications associated with ICP. Pregnant women should be made aware of the increased risks linked to continued pregnancy, including perinatal morbidity, maternal health complications, and stillbirth. In severe cases with very high bile acid levels (exceeding 100), an earlier delivery than 37 weeks may be warranted after administering steroid treatment. Mothers with ICP can safely breastfeed [48].

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Not applicable.

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