Hepatitis B in Pregnancy

The prevalence of hepatitis B surface antigen (HBsAg) amongst adult Singapore ***residents is between 3 to 4%****. Hence mother to infant transmission still remains an important issue.*

Mother to Infant Transmission

The risk of infants becoming HBsAg-positive carriers during the first 6 months of life was up to 63 % in infants born of HBsAg-positive mothers before the advent of hepatitis B vaccination. The main risk factors are maternal hepatitis B e antigen (HBeAg) status and hepatitis B viral load. Generally infants born to HbeAg-positive carriers have higher chronic HBV positivity rates compared to those born of HBeAg-negative mothers. Even so, 25–30% of infants born of HBeAg-negative mothers also became chronic carriers.

Immunoprophylaxis and Vacinnation for Infants born to Hepatitis B Carriers

Studies showed that the infant chronic HBV positivity state was reduced from 73.2 % to 21.0 % with vaccination alone, to 6.8 % after infants received vaccination and one dose of hepatitis B immunoglobulin (HBIG) and 2.9 % in infants who received vaccination plus multiple doses of HBIG.

A further study showed that only that 3.1 % of infants born of HBsAg-positive mothers were HbsAg positive at age 7–12 months after receiving HBIG with three doses of hepatitis B vaccine. All failures occurred in infants born of HBeAg-positive mothers with pre-delivery HBV DNA >6 log10 copies/ml.

ANTI-VIRAL THERAPY IN PREGNANCY

Assessment of a Hepatitis B Carrier

Maternal HBeAg, HBV DNA status, and ALT level should be discussed and assessed prior, during and after pregnancy. However, assessment for liver fibrosis or cirrhosis should be done only prior or after pregnancy. Fibroscan (transient elastography) is being increasingly used as an alternative to liver biopsy to help decide management. It measures liver elasticity, giving a liver stiffness measurement (LSM) in kilopascals (kPa), which indicates the level of liver fibrosis. Fibroscan take only a few minutes to perform and is acceptable to patients, giving instant results, is non-invasive, painless and highly accurate in HBV patients with severe fibrosis and cirrhosis. Unfortunately Fibroscan cannot be done during pregnancy or any condition where there is fluid in the abdomen such as ascites.

Indications to Start Treatment

The indications to start treatment include persistent hepatitis represented by an alanine aminotransferase (ALT) >2x upper limit of normal for more than 6 months, a hepatitis B flare, established fibrosis or cirrhosis or the development of hepatocellular carcinoma (HCC).

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Goals of Treatments

Short Term	Long Term
• HBV DNA viral suppression, • Normalisation of ALT • Histological improvement.	• Stop disease progression. • Prevent cirrhosis, liver failure and HCC.

Types of Treatment Available

Anti-viral therapy like Interferon (IFN) treatment was developed in the 1990's followed by pegylated interferon (PEG-IFN) and subsequently newer generations of nucleoside/tide analogues (NAs) which specifically target HBV DNA replication. IFN therapy is associated with more side-effects including flu-like symptoms, anorexia and weight loss, depression, bone marrow suppression and is not advised during pregnancy because of IFN's anti-proliferative effects. Patient on IFN therapy should be advised to use contraception.

MANAGEMENT

Before

Interferon (IFN)-based therapy (48 weeks treatment) has an advantage over NAs for HBeAg reactive carriers. 30% of individuals achieved HBeAg seroconversion 6 months after end-of-treatment. This is higher compared to one year on treatment with NAs. This results in a reduction in HBV viral load with an associated reduction in the risk of mother to infant transmission.

During

Treatment options should be discussed, taking into account the risks and benefits to the mother and fetus as well as issues regarding risks of maternal disease progression, maternal HBV flares, fetal development, vertical transmission of HBV, longer-term treatment and follow up and the next pregnancy.

Even with hepatitis B vaccination and HBIG, a proportion of infants can still potentially benefit from anti-viral treatment for mothers during pregnancy. Infants born to mothers with HBV DNA levels >6 log10 copies/ml are still at risk of immuonprophylaxis failure. Hence these mothers should be given the option of antiviral therapy.

Nucleoside/tide analogues (NAs), Telbivudine (LDT) and Tenofovir (TDF) are classified as category B drugs. Lamivudine (LAM), Adefovir (ADV), and Entecavir (ETV) are classified as category C drugs by the US FDA. Category B NAs (LdT and TDF) can be considered for mothers indicated for antiviral treatment during the first through third trimester of pregnancy.

To date TDF is the only NA without known viral resistance. Safety data from Antiretroviral Pregnancy Registries have also suggested that TDF does not appear to result in increased rates of birth defects with exposure during the first trimester.

The target population for short-term treatment using either LdT or TDF for pregnant females to reduce maternal HBV transmission should be mothers with HBV viral load above >6log10 IU/ml, starting maternal treatment between 28–32 weeks of gestation, after careful examination to exclude maternal systemic disorder and fetal anomalies. Stopping NAs therapy (at the time of or 4–12 weeks after delivery) is recommended in females without ALT flares and without pre-existing advanced liver fibrosis/cirrhosis.

After pregnancy

Continuation of treatment after delivery depends on maternal liver disease status and interval monitoring is suggested. Provided appropriate immunoprophylaxis has been given at birth, breastfeeding by HBsAg-positive women has not been shown to increase rates of peri-natal transmission. Breastfeeding may be allowed in patients on TDF.

HBsAg-positive women receiving antiviral therapy in pregnancy should be monitored closely for several months post-partum for hepatitis flares. Lifelong follow up should be offered to them for monitoring of complications such as liver disease and hepatocellular carcinoma.

IN SUMMARY

The management of hepatitis B in pregnancy remains complex and requires careful discussion with the mother and family. Though immunoprophylaxis has drastically reduced the burden of HBV through vertical transmission, there remains a subset of mothers with high viral load that should be able to make an informed choice about further anti-viral therapy that may further reduce that risk of transmission to their infant.