Prevention of HBV infection in infants born to high viraemic carrier

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Introduction

- Hepatitis B virus is a world wide burden
- It is a life long disease.
- It is a non curable but controllable disease.
- Our target is to prevent transmission by 2050 through mass vaccination.

Natural history

The natural history of chronic HBV infection can be schematically divided into five phases, which are not necessarily sequential.

- Immune Tolerant Phase
- Immune reactive phase
- Inactive carrier phase
- HBeAg negative CHB
- HBsAg-negative phase

Indications for treatment

- The indications are generally the same for both HBeAg-positive and HBeAg-negative CHB.
- This is based mainly on the combination of three criteria:
  - Serum HBV DNA levels
  - Serum ALT levels
  - Severity of liver disease

Vertical transmission of HBV

- HBsAg positivity at 6–12 months of life or HBV-DNA in an infant born to an infected mother.
- Studies suggest that serum HBV DNA levels can increase in late pregnancy and early post-partum, defined as the prior 90 days to 6 weeks post-partum.

Course of HBV

- Chronicity is about
  - 90% if infected at birth or first year of life.
  - 30%–50% aged 1–6 years.
  - 5%–10% if 6 years onwards
- Once chronic hepatitis is established, 15%–40% evolve to cirrhosis and HCC.
- HBV is also associated with extrahepatic disease.

Risk of transmission

- Without prophylaxis, the risk of HBV vertical transmission is high.
- The risk is highest in HBsAg ($10^{4-4.5}$IU/ml) and HBeAg positive viral load(>10^6 IU/ml):70%–90%
- Low for HBsAg-positive HBeAg negative mothers and low viral load : 10%–40%.

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- Despite adequate prophylaxis transmission may occur in high mater-nal viral load and HBeAg positivity.
- Maternal viral load-
  - $< 10^6$ IU/mL is not associated with transmission.
  - 10^6– 10^7 IU/mL is about 3%
  - 10^7– 10^8 IU/mL is about 7%
  - $> 10^8$ IU/m is about 8%
- Menstrual irregularity and severe nausea during first trimester is associated with high risk of transmission.

Mechanisms of MTCT

- Mother-to-child transmission of HBV can occur:
    1. Intra-uterine transmission
    2. Transmission during delivery
    3. Postpartum transmission
- Transmission during delivery is the most frequent method of vertical transmission.

Intrauterine transmission

- Cellular transmission, which refers to transmission of HBV.
- Serum/body fluid transmission.
- Genetic transmission, sperm and oocyte, could be infected by HBV and transferred to the embryo.
- The placenta acts as filter that is crossed only in case of high maternal viral load.

Delivery on different routes

- The delivery ways to maximally reduce the incidence of MTCT remains controversial.
- In the past, vaginal delivery was considered to increase the chance of transmission.
- Recent studies concluded that there is no difference between cesarean and vaginal delivery.

Management

HBV management in pregnancy is challenging.

These challenges :

- The failure of passive-active immunoprophylaxis in a small part of newborns
- The effect and necessity of periodical HBIG to mothers
- The safety of antiviral prophylaxis with NA
- The benefit of different delivery system
- The safety of breastfeeding.

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Currently available antivirals-

- Interferon ,Pegylated interferon
- Nucleoside nucleotide analogs- Lamivudine, Adefovir, Telbivudine, Entacavir, and Tenofovir.

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- Interferon and pegylated interferon are X catagory
- Lamivudine, entecavir, and adefovir are C catagory.
- Telbivudine and tenofovir are B catagory.

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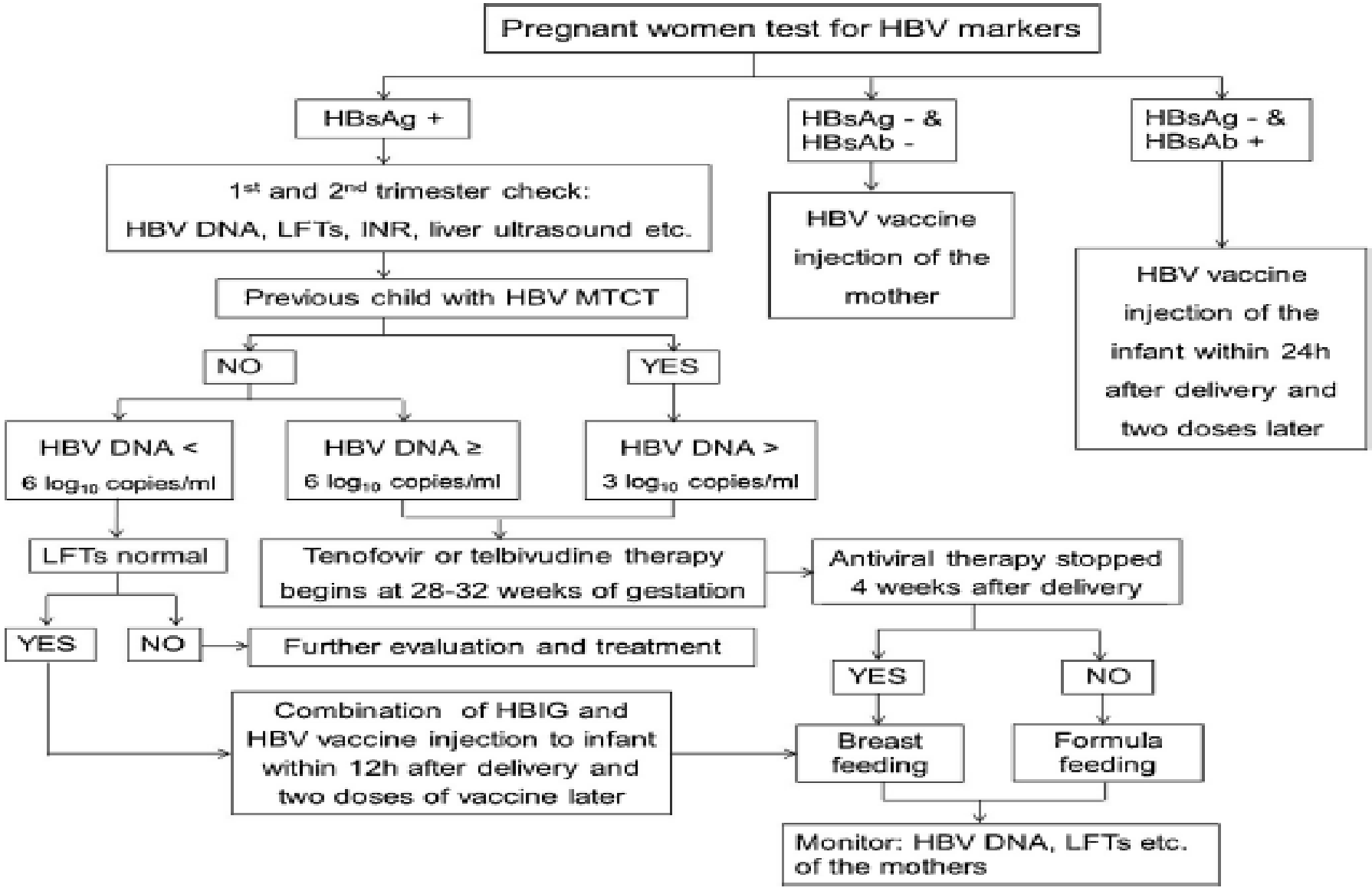
- Newborns of HBsAg-positive mother should receive HBIG and first dose of HBV vaccine within 12 hours
- The vaccine schedule is completed within first 6 months of life.
- For mother- category B drug should be started at 3rd trimester and continued up to 4 weeks after delivery.

Algorithm of treatment



Periodical HBIG administration during pregnancy

- Whether this approach during 3rd trimester impacts on preventing MTCT or not is controversial.
- Some studies showed it could activate the immune system by binding with HBsAg and decreased HBV replication and HBV DNA load to a certain extent.

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- But HBIG may cause HBV mutation, leading to immune resistance to HBV strains.
- This will result in failure of immunoprophylaxis and increased resistance of mutative virus to antiviral agent.
- Consequently, the periodic administration of HBIG to the mother to prevent vertical transmission is currently not recommended.

Active immunization with HBV vaccination

- Studies showed that 3 or 4 dose series of hepatitis B vaccine to newborn without HBIG has a protective efficacy of 70–80% in HBsAg and HBeAg positive mother.

Alternative NA

- In 2009 large randomized double blind placebo control study of lamivudine was done. But it showed no significant difference of efficacy.
- Currently lamivudine is no longer a first-line option for the treatment of chronic hepatitis B patients because of the high resistant rate.

Failure of immune prophylaxis

- The immune tolerance caused by low levels of HBV in neonate before HBV vaccine.
- The mutation of HBV.
- Low activity of IL-2 and related deficiency of immune functions.
- HLA- DP, HLA-DQ and HLA-DR and the genes unresponsiveness to HBV vaccine.

Take Home message

- Family planning should always be discussed with women of childbearing age before initiating HBV therapy.
- Screening for HBsAg in first trimester is strongly recommended.
- In childbearing age without advanced fibrosis who plans a pregnancy in near future, it may be prudent to delay therapy until child is born.
- Pregnant women with advanced fibrosis or cirrhosis, therapy with TDF is recommended.

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- Administration of tenofovir or telbivudine at 28–32 weeks of gestation is recommended in high viremia irrespective of ALT.
- Immunoprophylaxis within 12hours is proved to be successful in preventing approximately 90% of transmission.

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- About 8% of newborns suffered from HBV despite standard immunoprophylaxis
- The main reason is high viremia in mothers.
- Breast feeding is not contraindicated in-
  - HBsAg-positive untreated women
  - On TDF-based treatment
  - On immunoprophylaxis.

- There are still some controversy regarding-
  - Potential long-term side effects of antiviral agents to both mother and infant.
  - HBIG to mother during pregnancy.
  - Breastfeeding on antiviral therapy.


Thank
You