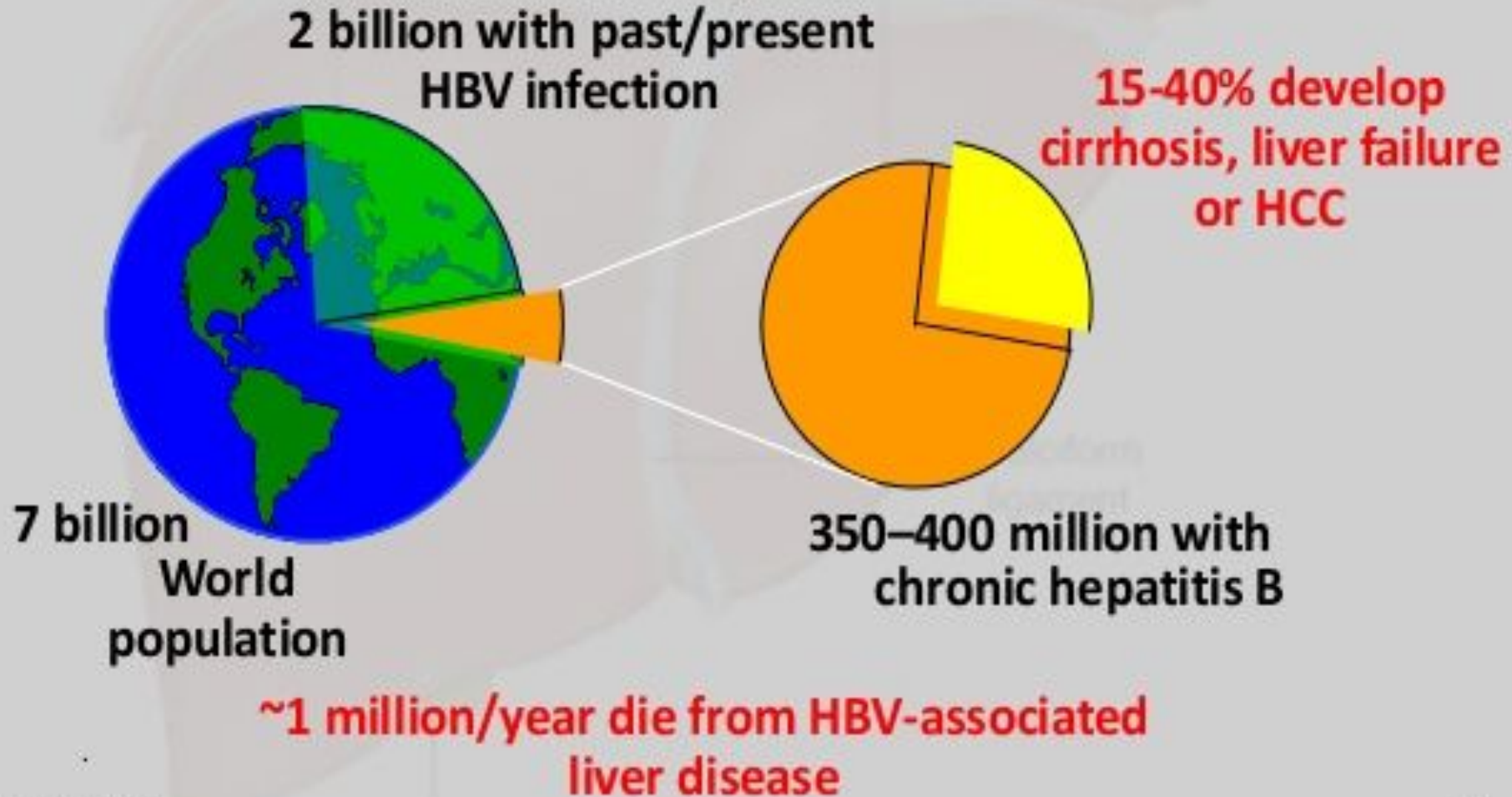


Global Impact of Hepatitis B





**Mother-to-Child
is the most common mode
of transmission for hepatitis B...**

...but it can be prevented!

HEPATITIS B: ARE YOU AT RISK?

HEPATITIS B IS A SERIOUS & DEADLY DISEASE



Hepatitis B virus infects people of all ages & as many as
2.2 M people
in the US are chronically infected



Up to 40%
of chronic infections lead to cirrhosis, liver failure, and liver and other cancers, which may lead to death

HEPATITIS B IS EASILY SPREAD



Hepatitis B is
50 to 100X more
infectious than HIV and can live
outside the body for **7+ days**
and still cause infection



2/3 of those living with chronic hepatitis B do not know they are infected but can still spread the virus to others



Hepatitis B can
be transmitted
from mother
to child at birth.

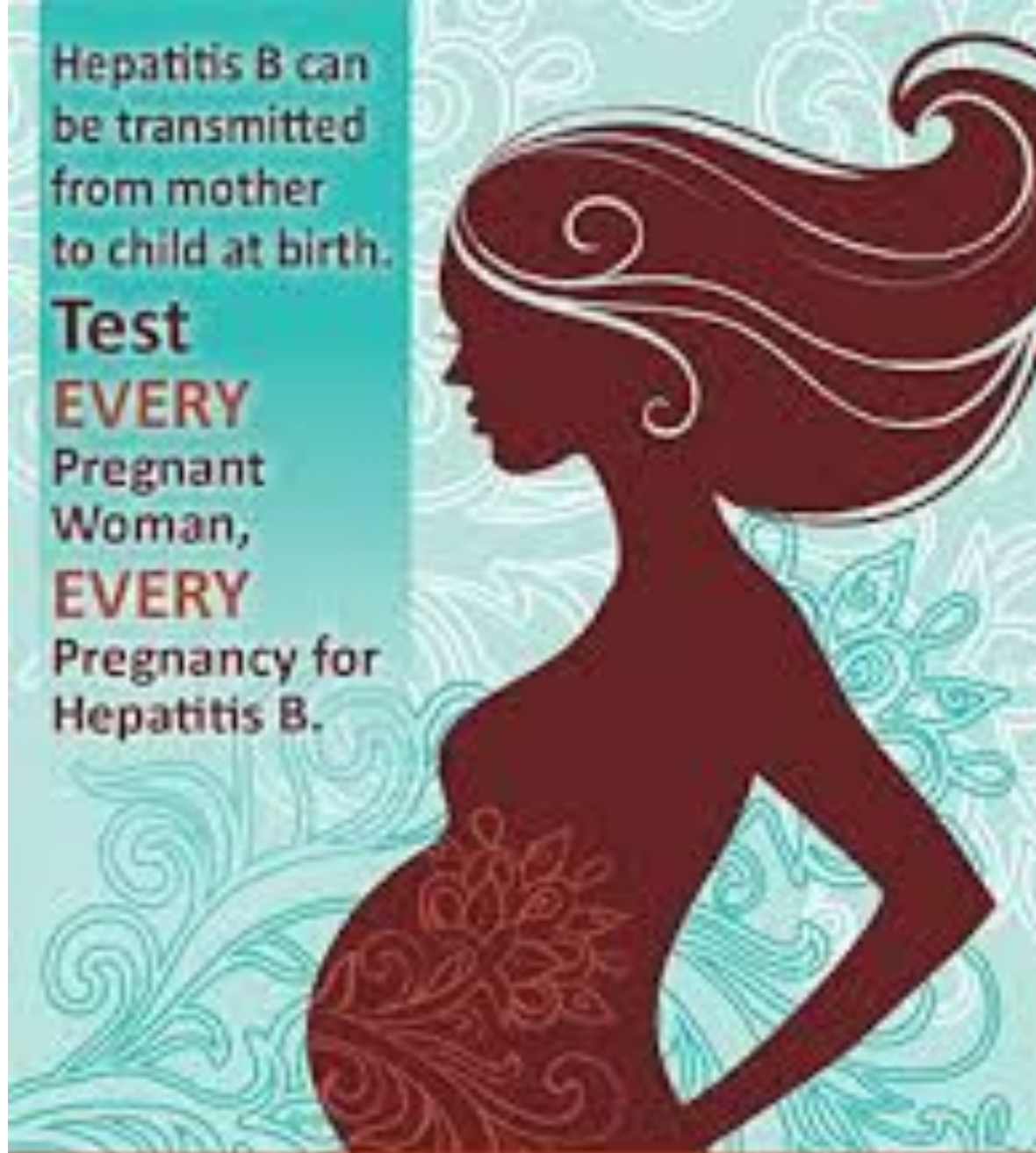
Test

EVERY

Pregnant
Woman,

EVERY

Pregnancy for
Hepatitis B.



Report HBsAg-positive results to the
Georgia Department of Public Health



IF YOU HAVE HEPATITIS B, PROTECT YOUR BABY

USE THIS CHART TO TRACK YOUR CARE AND YOUR BABY'S CARE

If you have hepatitis B, the virus can be transmitted to your newborn through your blood at birth. The baby can then carry this serious disease for a lifetime. To prevent infection, make sure your baby is protected with immunizations. Also, see your doctor regularly to take care of your hepatitis B and avoid liver damage.

DURING PREGNANCY

- ☐ Get blood tests.
 -  Hep B Viral Load
 - Liver tests
 - Hep B e antigen
- If your disease is severe, your doctor may talk to you about taking hepatitis B medication.
- ☐ Make sure your spouse and those living with you are tested for hepatitis B.
- ☐ See a doctor regularly for hepatitis B.



AT BIRTH

- ☐ Tell the staff at the hospital you have hepatitis B.
- ☐ Baby must receive 2 shots within 12 hours of birth to protect from infection.



One shot of hepatitis B immunoglobulin (HBIG)



1st shot of the hepatitis B vaccine

Once baby gets the HBIG shot and hepatitis B vaccine, it is safe to breastfeed. Hospital staff will give you an immunization card to track baby's shots. Bring this card to all of your baby's doctor visits.

AFTER DELIVERY

1-2 MONTHS

- ☐ Make sure your baby receives the 2nd shot of the hepatitis B vaccine.



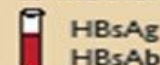
6 MONTHS

- ☐ Make sure baby receives the 3rd shot of hepatitis B vaccine. This shot should not be given before 6 months, or baby will not be protected.



9-15 MONTHS

- ☐ Make sure baby gets a blood test to check if he or she is protected after the shots. This is special for babies born to mothers with hepatitis B.



HBsAg

HBsAb

Check the test result:

- ____ Protected
- ____ Not Protected*
- ____ Infected

* If baby is not fully protected from hepatitis B, the doctor will repeat the vaccines.

IF YOUR BABY IS CARED FOR IN CHINA

- The caretaker must tell the new doctor that baby's mother has hepatitis B. It is very important to make sure the baby gets the 2nd and 3rd dose of the vaccine.
- Your baby must get the 3rd shot at 6 months and not earlier.
- Ask the doctor to test your baby by 15 months to check if he or she is protected from hepatitis B. This is not done for all babies, so the caretaker should request it because it is important for your baby. Keep a copy of the results.
- When your child returns to the United States, bring your child's vaccination records from China, and schedule a check up for your child. Immunization records are needed for children to enter to school.



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COMMUNITY HEALTH CENTER
五島康社區醫療中心

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Hepatitis B and Pregnancy

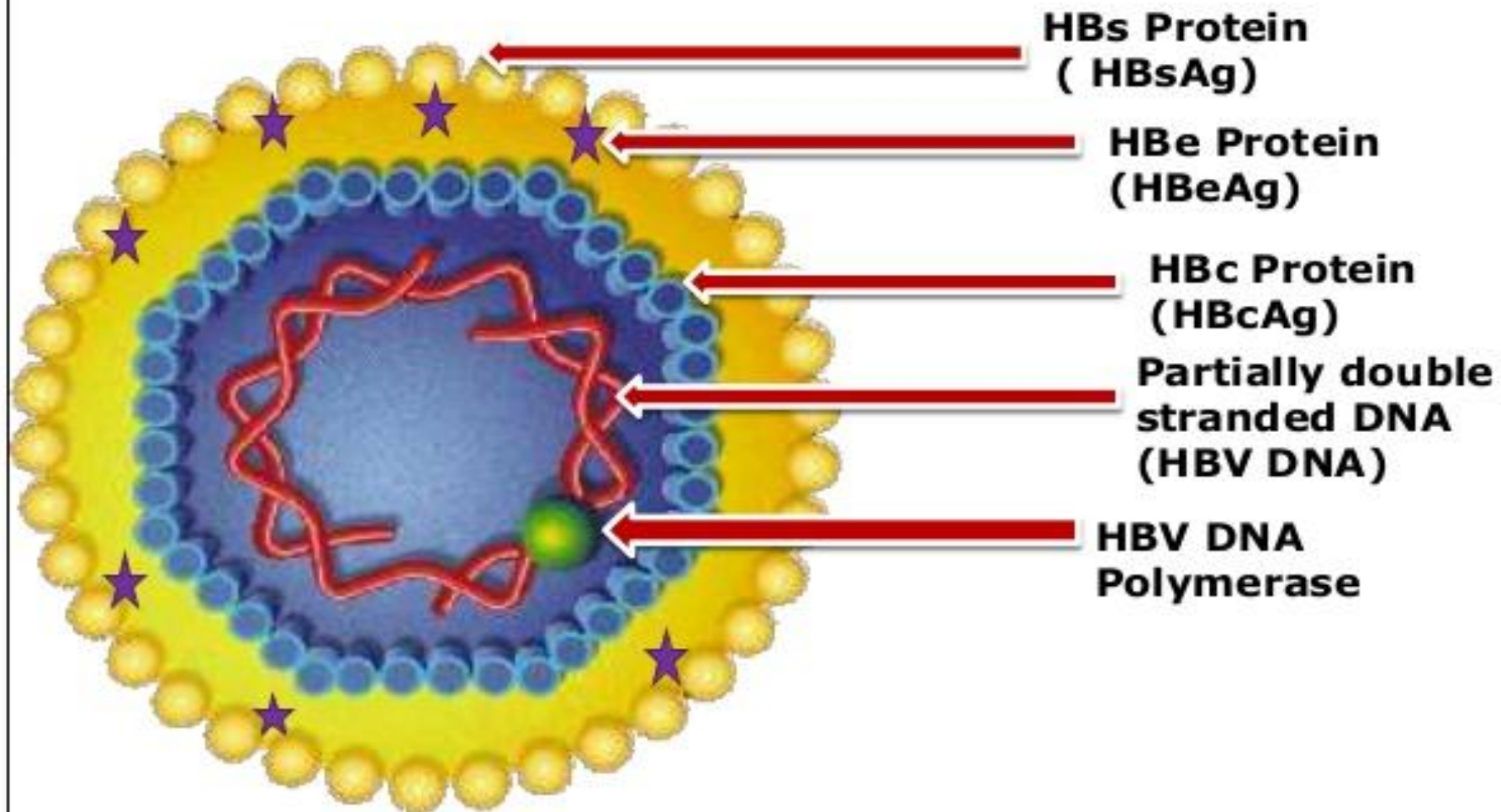
Mother

- Worsening of hepatitis before or during pregnancy?
- Worsening of hepatitis after delivery?
- Hepatitis B and other disorders during pregnancy

Infant

- Transmission of HBV?
- Teratogenicity of drugs?
- Risk of fulminant hepatic failure?
- Breast-feeding?

Structure of Hepatitis B Virus – wild type (HBeAg Positive)

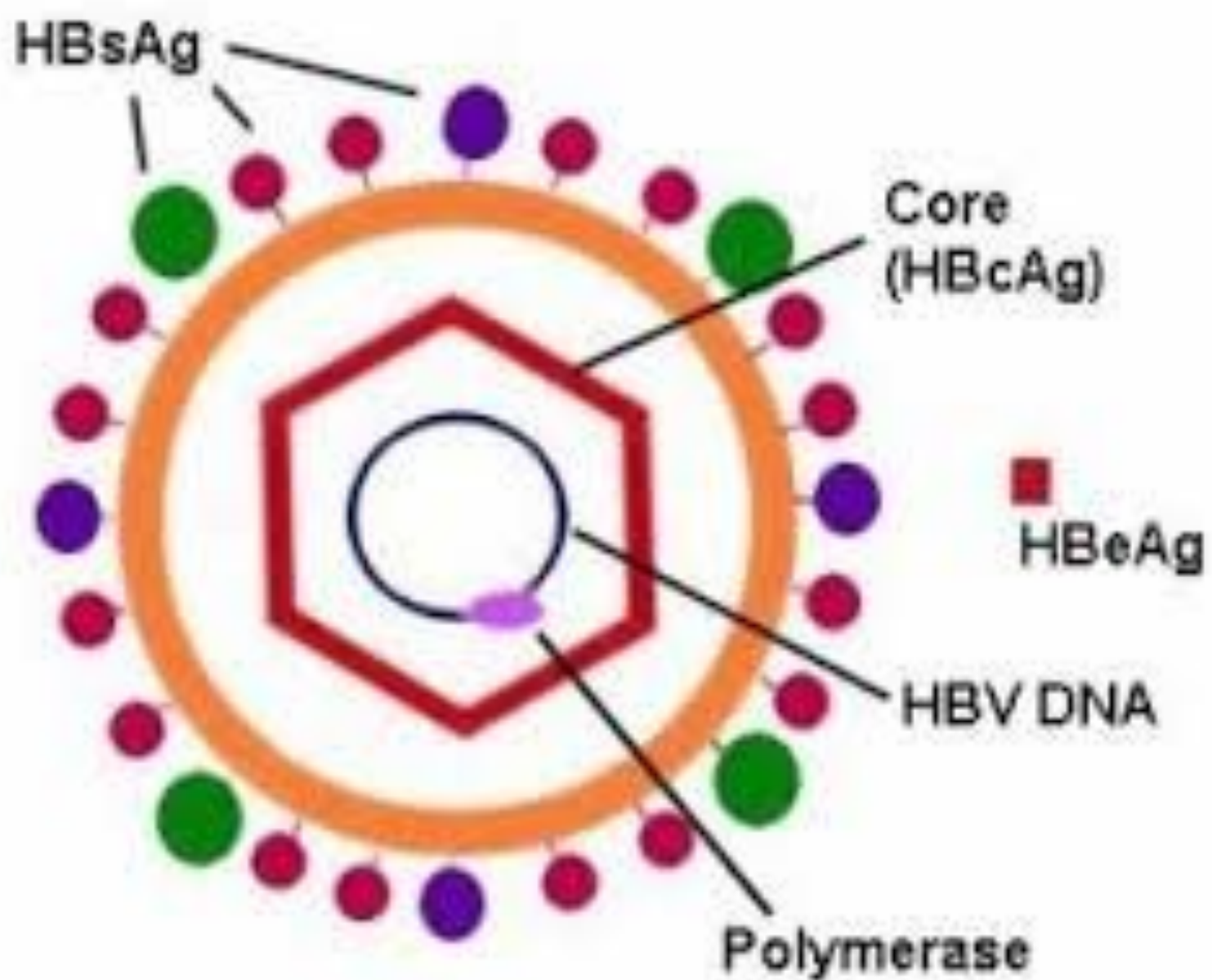


Hepatitis B

- in areas where hepatitis B virus (HBV) is endemic,
- **mother-to-child** transmission (MTCT) is the major route of infection of children.
- **Blocking** MTCT of HBV therefore would reduce its prevalence.
-

The World Health Organization (WHO)

- has set the goal of eliminating hepatitis as a threat to public health by **2030**
- which includes **reducing** the prevalence of hepatitis B surface antigen (HBsAg) among children to 0.1%.
- Mother-to-child transmission (MTCT) is the major route of hepatitis B virus (HBV) transmission, accounting **for 40% to 50% of chronic infections worldwide.**
- Therefore, **blocking MTCT of HBV will be the key step in achieving this goal.**



- The China Foundation of Hepatitis Prevention and Control organized a team of specialists in infectious diseases,
- **hepatology,**
- **immunology,**
- **obstetrics, and**
- **public health to develop an**

- **algorithm for interrupting MTCT of HBV, based on the most recent hepatitis B guidelines and latest evidence**

the core components of preventing MTCT.

- This algorithm comprises steps and has been adopted in clinical practice in China.
- Four aspects
 - 1-screening
 - 2- antiviral intervention during pregnancy
 - 3-immunoprophylaxis
 - 4- postvaccination serologic testing

passive and active immunization in newborns

- Although the combination of
- passive and active immunization in newborns of hepatitis B surface antigen–positive mothers reduces MTCT of HBV,
-
- this **immunoprophylaxis** cannot completely eradicate MTCT

- **In the past decade**

- administration of antiviral agents to pregnant women has been shown to be safe and effective in reducing MTCT of HBV in combination with immunoprophylaxis.

Aiming to achieve zero MTCT, this algorithm recommends

- the **use of antivirals** during **pregnancy** by women with high viral loads.
- Preventing MTCT is key to **achieving the goal of eliminating HBV** as a
- public health threat by **2030**.
- **Implementation and enhancement**
- of the standardized algorithm for
- pregnant women with chronic HBV infection and their infants is urgently needed to prevent MTCT.

The mainstay of preventing hepatitis B acquisition at birth

- comprises at least 3 doses of hepatitis B vaccine, including a birth dose administered in a timely manner,(within **24** hours of birth).
- **Active-passive immunoprophylaxis** through use of hepatitis B immune globulin (HBIG) is recommended among infants born to women with chronic HBV infection.⁴

- Although recent studies have suggested that vaccine alone
- may be as effective as the combination of vaccine and HBIG in preventing infection among neonates born to HBsAg-positive/hepatitis B e antigen (HBeAg)-negative women,
- the current standard recommendations include the use of HBIG for the prevention of MTCT.

- .

- **Known factors that increase the risk of MTCT include**

- 1- HBeAg positivity
- 2-high viral load among pregnant women
- 3- instrumental deliveries at birth

Several sets of guidelines

- American Association for the Study of Liver Diseases,
- the European Association for the Study of the Liver,
- the Asian Pacific Association for the Study of the Liver,
- the National Institute for Health and Care Excellence,
- **recommend consideration of antiviral use among pregnant women with chronic HBV infection.**

- **The practice protocol for the care of HBsAg-positive pregnant women and their infants is as follows.**

Testing and Diagnosis

- Following the current national recommendations of the National Health Committee,
- **all pregnant** women should be screened for
- hepatitis B
- syphilis
- human immunodeficiency virus at the first prenatal examination and/or as early as possible during antenatal care.

.HBS Ag status

- If the test result for HBsAg is negative,
- women should be counseled regarding their result and receive the usual standard of care for pregnant women.

If the HBsAg test is positive

- which indicates maternal HBV infection,
- the whole set of HBV serologic markers should be tested to assess the status of HBV infection.
- **HBsAg-positive pregnant women** should be managed jointly by an obstetrician for the well-being of the fetuses and women and by a hepatologist/gastroenterologist or infectious disease specialist for their hepatitis disease status during
 - pregnancy
 - labor
 - delivery
 - postpartum period.
- Continued follow-up evaluation after delivery will be required.

Initial Assessment (Baseline) and Management Decisions

- The Group recommends
- staging of liver disease status for HBsAg-positive pregnant women to determine the degree of liver injury.
- **Baseline tests include**
- 1- maternal HBV viral load (HBV DNA)
- 2- HBV serologic markers
- 3-liver function tests
- 4-upper abdominal ultrasound.
-

Management decisions should consider the following.

- First
- in **HBeAg-positive pregnant women** with HBV DNA levels greater than 20,000 IU/mL or
- **HBeAg-negative pregnant women** with HBV DNA levels greater than 2000 IU/mL and significant hepatic activity,
- alanine aminotransferase (ALT) level $\geq 5\times$ the upper limit of normal (ULN) (excluding other potential etiologies),
- or cirrhosis,
- the consideration in starting antiviral therapy is the woman's health

- **. The drug of choice is TDF, which should be prescribed after**
- 1- clinical assessment,
- 2- counseling,
- 3- patient education,
- 4- and receipt of informed consent by specialists in hepatology or infectious diseases.
- **The decision to start antiviral treatment and the plan for patient management should be communicated to the obstetric team.**
- --

Second, in pregnant women who are

- **HBV DNA positive and who have ALT levels ≥ 2 but less than $5\times$ ULN, antiviral therapy can be postponed.**
- Close monitoring based on clinical symptoms and serology is required throughout pregnancy.
- **The Group recommends, at a minimum, liver function monitoring every 4 weeks during pregnancy.**

- If ALT level increases to $\geq 5 \times$ ULN, treatment decisions should follow first point
- if the ALT level is reduced to $< 2 \times$ ULN, treatment management should follow
- third point; if the ALT level remains within the range of ≥ 2 to $< 5 \times$ ULN, clinicians should consider starting antiviral treatment at gestational week 24 using TDF after patient education and obtaining informed consent.

Maternal viral load	Perinatal transmission rate
< 200,000 IU/mL (Log 5.3)	0%
200,000 – 1,000,000 IU/mL (Log 5.3 – 6)	3.20%
1 – 2,000,000 IU/mL (Log 6-6.3)	6.70%
> 2,000,000 IU/mL (> Log 6.3)	7.60%

- **Third**, in pregnant women found to have viremia, an ALT level $<2\times$ ULN, and **no cirrhosis**, there is no indication to initiate antiviral therapy.
- Clinical and liver function monitoring is recommended.
- If there are signs of progression of liver disease (that is, ALT level $\geq 2\times$ ULN) during the course of the pregnancy, treatment considerations should follow first or second point.
- accordingly. In addition, total bilirubin and prothrombin activity should be tested to evaluate the severity of liver disease.

Management During Pregnancy

- in pregnant women with
- **normal or slightly increased ALT levels,**
- HBV DNA level should be quantified with the sensitive method of real-time polymerase chain reaction in the second trimester.
-
- For the prevention of HBV MTCT, antiviral treatment should be considered based on HBV DNA quantification.

- **If HBV DNA level is greater than 2×10^6 IU/mL,**
- antiviral treatment with either TDF or LdT (high quality, strong recommendation) should be administered after patient education and informed consent at gestational weeks 24 to 28.
- The risks and benefits and the limited evidence for this approach should be discussed with the patient.
- The benefit of antiviral treatment is to protect the newborns from HBV infection and to control hepatitis activity in mothers with increased ALT levels

- It has been reported that the rate of MTCT can be **decreased** further
- by **antiviral treatment in HBsAg-positive mothers** during late pregnancy.
- At the same time, the patients should be informed about potential risks related to the administration of antivirals, such as
 - **side effects of drugs**
 - (renal injury, hypophosphatemia, myopathy),
 - drug-resistant mutations,
 - potential harm to the fetus,
 - postpartum hepatic flare

TDF and LdT

- . Generally, pregnancy category B drugs such as TDF and LdT are safe to use during pregnancy,
- and antiviral treatment with TDF or LdT has no influence on congenital abnormalities or neonatal growth percentiles.
- in utero exposure to TDF resulted in a 12% reduction in total mean whole-body bone mineral content (56.0 vs 63.8 g, respectively; $P = .002$).
- Moreover, the rate of postpartum hepatic flare was reported to be 40% to 50% in mothers who stopped antiviral treatment

I. Antivirals

Drug	Pregnancy Category
IFN alfa-2b	C
PegIFN alfa-2a	C
Adefovir	C
Entecavir	C
Lamivudine (Epivir)	C
Telbivudine (Tyzeka)	B
Tenofovir (Viread)	B

- Accumulating studies have shown that treatment using TDF or LdT during the third trimester is effective and safe for the prevention of MTCT in mothers with high viral loads and this approach has been recommended by major guidelines.

- In pregnant women with very high baseline viral loads ($\geq 1 \times 10^8$ IU/mL),
- earlier initiation of antiviral therapy may be necessary to achieve viral suppression below the recommended threshold.
- **Before delivery**, HBV DNA quantification should be repeated to evaluate the efficacy of antiviral therapy and the risk of MTCT.

- if the HBV DNA level is $\leq 2 \times 10^6$ IU/mL,
- **antiviral therapy is not recommended.**

Considering that the **threshold** of antiviral therapy to prevent MTCT is **variable** among current guidelines and MTCT still may occur in pregnant women with lower HBV DNA levels

options for antiviral therapy

- options for antiviral therapy should be provided to those with HBV
- **DNA levels $\leq 2 \times 10^6$ IU/mL and high-risk factors for MTCT,**
 - 1-such as history of MTCT
 - 2- threatened abortion
 - 3- threatened premature labor
 - 4- and indications of invasive procedures

Societies	Threshold of HBV DNA level	Initiation time	Cessation time	Antivirals	Reference
AASLD (2018)	$>2 \times 10^5$ IU/mL	28–32 wk	At birth to 3 months	TDF	17
EASL (2017)	$>2 \times 10^5$ IU/mL	24–28 wk	Up to 12 weeks after delivery	TDF	18
APASL (2015)	$>6-7 \log_{10}$ IU/mL	28–32 wk	At delivery	TDF LdT	19
CMA (2015)	$>2 \times 10^6$ IU/mL	24–28 wk	At delivery	TDF LdT LAM	25
NICE (2013)	$>10^7$ IU/mL	The third trimester	4–12 weeks after birth	TDF	20

Delivery Management

Mode of Delivery

- The mode of delivery should follow the usual obstetric indications.
- Routine cesarean section is not recommended for the prevention of HBV transmission.
- There is no clear and strong evidence to support cesarean section as the mode of choice for preventing MTCT of HBV.

- Among cases of HBV MTCT, **a large proportion** occur around labor and delivery, particularly with risk factors including
 - 1- high maternal viremia,
 - 2- transfusion of the mother's blood to the fetus during labor contractions,
 - 3- infection after rupture of membranes,
 - 4- and direct contact of the fetus with infected secretions or blood from the maternal genital tract.
- **At the time of delivery, clinical assessment of HBV-infected pregnant women should include liver function status**

With consideration for the safety of the fetus

- **procedures that break the skin and mucosal barrier should be avoided as much as possible:**
 - 1- including fetal scalp electrodes,
 - 2- fetal scalp blood sampling,
 - 3- and vigorous suctioning of the newborn's airway at birth.

Instrumental delivery

such as the use of

1- vacuum extraction

2- forceps to expedite delivery during the second stage of labor, should follow obstetric indications.

- There is a small risk of traumatizing the fetal skin and risking transmission of HBV to the infant.

Care of the Newborn

- **Standard precautions** should continue when handling the newborn.
 - 1- Visible blood,
 - 2- mucus,
 - 3- amniotic fluid on the surface of the neonate and the cord should be gently wiped off.
- **Standard procedures** for cord cutting should be followed.
- **Immunoprophylaxis** to be delivered at birth, including the hepatitis B vaccine and HBIG, should be provided.
- **The skin at the injection** site should be cleaned with an alcohol swab before the injection is administered.

Discontinuation of Antivirals

- the **appropriate time** to discontinue antivirals still is controversial among current guidelines because the **evidence** on this issue is not sufficient.
- In most studies on antiviral therapy during pregnancy to prevent MTCT, maternal antiviral therapy was discontinued at **1 to 3 months** after delivery to avoid ALT flares.

Discontinuation of Antivirals

- For pregnant women who have **normal ALT levels** and receive antiviral therapy to prevent MTCT during pregnancy
- drugs can be **discontinued immediately after delivery** .
- **Close monitoring** of maternal ALT levels is warranted after withdrawal of antivirals because postpartum hepatitis may occur.

.

- **the European Association for the Study of the Liver guidelines recommend:**
- that antiviral therapy be stopped up to 12 weeks after delivery for pregnant women who receive antivirals to prevent MTCT.
- However,
- extension of antiviral therapy for several weeks or months has not been shown to significantly prevent the occurrence of a postpartum hepatitis flare.

- Therefore, the Chinese Medical Association guidelines
- suggest that maternal antiviral therapy can be **discontinued at delivery** and that regular monitoring of ALT levels should be performed to detect postpartum hepatitis flares.
- It was reported that ALT flares occurred more frequently in mothers who previously had taken TDF than in those who had not received TDF (45% vs 30%).

- Although **postpartum hepatitis** often is **mild** in severity and usually **resolves spontaneously**,
- **severe ALT flares were observed in approximately 5% of mothers after discontinuation of antivirals.**
- **Care** should be taken to address the possibility of severe hepatitis, even fulminant hepatitis.
- Because the existing evidence is limited and insufficient, well-designed studies are needed to ascertain the appropriate time to stop antiviral therapy.

- For pregnant women who experience hepatitis flares and start antiviral therapy for their hepatitis, **antiviral treatment should not be stopped after delivery.**
- Such women should continue treatment for hepatitis under the direction of hepatologists/gastroenterologists or infectious disease specialists.

Neonatal Immunoprophylaxis

- Within **12 hours** after delivery, preferably as soon as possible,
- 100 IU HBIG should be administered intramuscularly in the anterolateral thigh or deltoid muscle .
- A prospective cohort study in China showed that 1 birth dose of 100 IU combined with the 3-dose hepatitis B vaccine series would be sufficient to prevent MTCT of HBV in infants born to HBeAg-positive mothers.

- At the same time, the first dose of the recombinant yeast hepatitis B vaccine (10 µg/0.5 mL) should be administered in the anterolateral thigh or deltoid muscle on the opposite side of the body.
- The other 2 doses of 10 µg/0.5 mL hepatitis B vaccine are scheduled at **1 and 6 months** of age.

- **timely administration** of HBIG and hepatitis B vaccine is critical for interrupting MTCT.
- The Centers for Disease Control and Prevention recommend that the **birth dose of HBIG and hepatitis B vaccine be given within 12 hours after birth.**
- Any delay **beyond 48 hours** in the administration of HBIG has a significant impact on the rate of MTCT.
- Timely administration of the first dose of hepatitis B vaccine can provide **early postexposure protection and enhance compliance in completing the vaccination series.**

A delayed vaccination schedule also is possible.

- If the originally scheduled **second dose** of the hepatitis B vaccine is missed by up to **3 months**,
- this dose should be injected **as soon as possible**,
- and the **third dose** of vaccine should be provided at **6 months**.
-

- If, however, the second dose is delayed by more than 3 months from the planned visit,

the dose should be **given as soon as possible**,

and **the third dose** should be scheduled for **2 months later**.

For preterm and low-birth-weight infants (<2000 g)

- 100 IU HBIG plus hepatitis B vaccine (10 µg/0.5 mL) should be administered within 12 hours,
- with 3 subsequent doses of vaccine (10 µg/0.5 mL each) scheduled at **1, 2, and 7 months of age.**
- Infants with unknown maternal HBsAg status should be treated as infants born to HBsAg-positive mothers.

- Those children's mothers should be tested for HBsAg as soon as possible.
- If the mother is HBsAg negative, the **3 doses of vaccine** can be started at **1 month of age** or postponed until just before hospital discharge.
- The vaccination scheme still should be administered according to the 0-1-6 months schedule.

Breastfeeding

- Mothers who were not treated with antivirals during pregnancy are encouraged to breastfeed if their newborns have received combined immunoprophylaxis composed of HBIG and hepatitis B vaccine (B1).

For mothers on antiviral treatment for the prevention of MTCT

the antiviral treatment can be discontinued after delivery,

and breastfeeding then can be allowed if the newborns have received

combined immunoprophylaxis.

If mothers receive antivirals to treat chronic hepatitis B

- and continue treatment after delivery, breastfeeding is not contraindicated (low quality, weaker recommendation).
- It has been reported that in the **breast milk of TDF-treated mothers**, the drug is present only at low concentrations
- and its oral bioavailability is limited; thus, infants are exposed to only a minuscule amount of TDF.

Follow-Up Evaluation of Infants

- Infants born to HBsAg-positive mothers should be followed up for completion of hepatitis B vaccination and postvaccination serologic testing (PVST).
- PVST is important for evaluating the effect of hepatitis B immunization and identifying HBV infection in infants
- . WHO and the Centers for Disease Control and Prevention recommend PVST for infants born to HBV-infected women

- . PVST should be performed after completion of the hepatitis B vaccine series and at least 1 month after the last hepatitis B vaccine dose.
- Because of possible interference of the HBIG injection at birth and a decrease in antibody to hepatitis B surface antigen (anti-HBs),
- PVST should not be performed before completion of hepatitis B vaccination or after 12 months of age

Assessment of Postvaccination Serologic Testing for Hepatitis B Virus–Exposed Infants

- PVST examines 2 markers, namely, HBsAg and anti-HBs (antibody levels), which allow clinicians to determine whether an infant is immune and protected, infected, or uninfected and nonimmune.
- Quantification of anti-HBs antibody levels will help clinicians determine whether an infant is protected; the threshold of protection is defined as ≥ 10 mIU/mL.

- HBsAg-positive infants should be referred for appropriate clinical care and follow-up evaluation and their parents counseled.
- HBsAg-negative infants with anti-HBs levels ≥ 100 mIU/mL are protected against hepatitis B and do not require further medical management.

- **HBsAg-negative infants** with anti-HBs less than 10 mIU/mL should have their HBV DNA levels tested to rule out the possibility of **occult HBV infection**.

If HBV DNA is undetectable, these infants should be revaccinated with a further 3 doses of hepatitis B vaccine (10 µg/0.5 mL) and undergo PVST 1 to 2 months after the final vaccine.

- An anti-HBs antibody level of ≥ 100 mIU/mL indicates a **good immune response** with protective immunity,
- while an antibody level of **less than 10 mIU/mL** indicates **no significant response or immunity.**
- An antibody level of ≥ 10 to < 100 mIU/mL after vaccination indicates **low response.**

- Among infants born to HBsAg-positive mothers, the rate of nonresponse/low response to hepatitis B vaccine was reported to be **22.4% to 30.2%**, compared with **5% to 10%** in the **general infant population.**

- The risk factors of nonresponse/low response to hepatitis B vaccine include
 - 1-high HBV DNA level
 - 2-premature labor
 - 3- low birth weight
 - 4- type of hepatitis B vaccine, and so forth.

- Several studies have shown that additional doses of hepatitis B vaccine could induce: a robust anti-HBs response in most low-responding infants.
- An additional single dose of **10 µg** hepatitis B vaccine should be administered to **low-responding infants**,
- given that the immune response of low-responding infants might be **unstable** and the **potential risk of horizontal** infection still exists under the circumstances of close contact between mother and infant.

Follow-Up Evaluation of Mothers After Delivery

- Mothers on antiviral treatment after delivery should be followed up according to the protocol for general chronic hepatitis B patients.
- **Liver function and HBV DNA level should be checked every 3 months.**
- HBV serology, α -fetoprotein tests, abdominal ultrasound, and transient elastography should be performed at 6-month intervals.

- Liver function and **HBV DNA level** should be checked at **6 to 8 weeks** postpartum in mothers who discontinue antivirals after delivery.
- If liver function is normal, monitoring should be continued at intervals of 3 to 6 months.
- If liver function is abnormal at 6 to 8 weeks after delivery, patients should be managed following the recommendations of the Guideline of Prevention and Treatment of Chronic Hepatitis B .

- Mothers not on antiviral treatment may experience ALT flares or exacerbation after delivery.
- Liver function should be monitored at postpartum weeks 3 to 4 and 9 to 12, especially in **mothers with increased ALT and detectable HBV DNA** levels at delivery.

Practice Considerations

- Prevention of new infections of hepatitis B among infants is key to ensuring a generation free of hepatitis B.
- The current standards of care for HBV prevention (3 vaccines and HBIG), are highly effective, and additional interventions should be considered for HBV-infected women who are HBeAg positive and/or have high viral loads.

- In the implementation of these clinical practice protocols,
- physicians and the team caring for the well-being of the pregnant women and her fetus should establish good communication for multidisciplinary care.
- **Local hospital protocols** should be established to provide a reliable patient clinical pathway between hospital departments to ensure seamless care and good patient education .