Hepatitis B virus infection in pregnant women and transmission to newborns

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1. Introduction

Hepatitis B infection is a worldwide problem. Approximately, there are 350 million chronically infected people worldwide. India represents the second largest pool of chronic hepatitis B virus (HBV) infection in the world with an estimated 40 million infected people. Vertical transmission is known to be the leading cause of infection and perinatal infection is associated with a very high rate of chronicity (up to 90%). Hepatitis B e antigen (HBeAg) positivity indicates that replicative form of HBV may play a role in immunotolerance in utero by crossing the placenta. Up to 40% of chronically infected individuals will die prematurely from complications such as acute liver failure, cirrhosis and hepatocellular cancer. In case of HBeAg positivity and high viral load of mother, HBV immunoglobulin is preferably given along with HBV vaccination. Antiviral therapy is recommended for use in the third trimester of pregnancy to reduce the perinatal transmission of HBV; however, use of antiviral therapy should be individualized during pregnancy. Addressing perinatal transmission through the use of immunoprophylaxis can help contain the spread of HBV. Pregnant mothers with chronic hepatitis B have unique challenges and require specialized management during and after pregnancy. This review will look at the screening of pregnant women for hepatitis B, passive and active immunoprophylaxis, mechanisms of perinatal viral transmission and therapeutic considerations in pregnancy including possible teratogenicity and efficacy of medication. Other issues such as the mode of transmission and breastfeeding will be covered.
through contact with infected body fluids[4]. Perinatal vertical transmission is the most common mode of transmission worldwide[5,6]. In households of a chronically infected individual, HBV infection can occur via person-to-person, nonsexual contact[7].

In Southeast Asia and China, the prevalence of HBV infection among women of child-bearing age is as high as 10%-20%[8]. In India, the prevalence of chronic HBV infection in pregnant females is 0.82%-9% and during pregnancy, hepatitis B virus infection presents the risk of mother-to-child (vertical) transmission. To analyze the source of acquisition of HBV infection in chronic HBV infected patients, mothers of 384 chronic hepatitis B index patients were screened for HBV infection. The mothers of 40.1% index patients were positive for hepatitis B surface antigen (HBsAg). The mothers of 34.1% index patients were positive only for antibodies (total anti-HBc and/or anti-HBe), indicating that the mothers were exposed to HBV infection some time in the past[10]. These data provide substantial evidence of present or past HBV infection in mothers of chronic HBV patients, suggesting possible perinatal transmission. It could be possible that one third of mothers, who were initially HBsAg positive, could have cleared the infection during post-partum period and remained positive only for HBV antibodies[10]. Therefore, vertical transmission of hepatitis B virus could be one of the main causes of chronic HBV infection in our country.

The neonates born to mothers infected with chronic hepatitis B, have 90% risk of acquiring chronic HBV infection and its persistence[11]. In contrast, when HBV is acquired during adulthood, only 5%-10% of adults develop persistent chronic HBV infection[12]. Most of the developed countries screen all pregnant women for HBV infection, however, in the developing countries it depends upon the risk factors. In India, there is no consistent policy of screening the infection, however, in the developing countries it depends upon the risk factors. In India, there is no consistent policy of screening the pregnant women across the country. A meta-analysis of prevalence of hepatitis B in India showed the prevalence rate in general population is 2.4%[13]. However, the prevalence rate of HBsAg positivity in pregnant women varied from 1%-9% in different parts of the country and hepatitis B e antigen (HBeAg) positivity rates among them varied from 4.8%-66.7%[13].

A large single centre study from North India of 20104 pregnant women showed a chronic HBsAg positivity rate of 1.1%[14]. Majority of pregnant women with viral hepatitis B are considered as chronic hepatitis B infected but a few may develop acute hepatitis in the third trimester of pregnancy resulting in 1% fulminant hepatitis[15,16]. During pregnancy, acute viral hepatitis involves a particular risk both for the mother and the baby.

The risk of maternal-infant transmission is related to the HBV replicative status of the mother which correlates with the presence of HBeAg as 90% of HBeAg-positive mothers transmit HBV infection to their offspring compared to only 10%-20% of HBeAg-negative mothers[17]. The high frequency of perinatal transmission in endemic areas is probably related to the high prevalence of positive HBeAg in women of reproductive age in these countries. Studies have shown that the rate of HBeAg seroconversion during the first 20 years of life is relatively slow, leaving many women of child bearing age who have contracted HBV infection in their early childhood still highly infectious to their infants[18].

2. Effect of HBsAg and HBeAg on pregnancy

HBV infection does certainly affect the outcome of pregnancy and influence spontaneous abortion, stillbirth, or prematurity. Increased frequencies of reproductive casualties were reported in pregnant women with acute or chronic hepatitis B infection[19]. With HBV infection, the incidence of preterm birth observed was quite high, around 21.9% vs 12.1% in healthy controls[20].

The gestational diabetes and antepartum haemorrhage are also associated with chronic hepatitis B infection[21]. In a case-control study, HBeAg positivity was proved to be more important with high HBV DNA levels in transmission of HBV to infants[22]. HBeAg positivity indicates replicative form of HBV may play a role in the immunotolerance in utero by crossing the placental barrier[23]. In HBV genotype C, HBeAg seroconversion is longer, which may be the reason for higher perinatal transmissions in this genotype[24]. Therefore, in prenatal screening of pregnant women, it is important to check the HBeAg status along with HBsAg.

3. Mother to child transmission (MTCT)

The transmission of infections from mother to offspring is traditionally known as perinatal infection. By definition, perinatal period begins from the 28th week of gestation and ends at 28 days after delivery. Therefore, the term “perinatal transmission” does not actually include infections that occur before or after this time period and thus can be replaced by the term “(MTCT)” which takes account of all HBV infections contracted before birth, during birth and in early childhood; the importance of which as a group is their remarkably greater risk of chronicity compared to infections acquired later in life[25]. Theoretically, there are three possible routes for transmission of HBV from an infected mother to her infant[26]: 1) Transplacental transmission of HBV in utero; 2) Intrapartum transmission; 3) Postpartum transmission during care or through breast milk.

3.1. Transplacental transmission of HBV in utero

The prenatal (intrauterine) route of HBV transmission is currently considered the chief culprit behind this failure. The exact mechanism for perinatal transmission of HBV is not fully elucidated yet, however, various possibilities are hypothesized.

3.1.1. A breach in the placental barrier

Of the two secretory proteins: HBsAg and HBeAg, HBsAg does not usually cross the placenta; however, small sized HBeAg passes through the placental barrier even with low maternal viral load titre[27,28]. In newborn, transplacental HBeAg can be detected at one month of age, but it would disappear before 4 months of age. However, in a few infected newborns with HBV viral titres, persistent detection of HBeAg for more than 4 months strongly indicates HBV chronicity[29,30]. It is also observed that anti-HBc (antibodies to
core antigen) positivity can be detected more than anti-HBe in the babies born to hepatitis B infected mothers[27,28]. Therefore, anti-HBe till one year of age and anti-HBc till two years of age represent the transplacental maternal antibodies to the virus and may not be an indicator of present active or past HBV infection in babies born to hepatitis B infected mothers.

Hepatitis B envelope antigen spillage through placenta induces HBV specific T cell tolerance in uterus[31] and intrauterine infection could be the main cause of the failure of immunoprophylaxis[32-34]. However, there are several evidences to show that the incidence of intrauterine transmission is rare and only happens in case of placental leakage[35,36]. The transplacental leakage of HBeAg-positive maternal blood, which is induced by uterine contractions during pregnancy and the disruption of placental barriers (such as threatened preterm labor or spontaneous abortion), is one of the most likely routes to cause HBV intrauterine infection[37]. It has been shown that amniocentesis inoculates the intrauterine cavity with maternal blood because the needle traverses the abdominal and uterine wall. However, HBV transmission during amniocentesis appears to be rare, particularly in mothers who are HBeAg-negative and when the procedure is done by using a 22-gauge needle under continuous guidance[38].

Infants born to HBeAg-positive mothers are likely to be infected and progress to chronicity, however, infants born to HBsAg positive mothers develop acute hepatitis and are less likely to progress to chronicity[28]. In north India, HBeAg positivity was 7.8%, and risk of perinatal transmission was 18.6% from HBsAg positive mothers vs. 3% among infants of HBsAg-negative mothers[39,40].

### 3.1.2. Placental infection and transplacental transmission of HBV

Placental infection in a fetus with intrauterine HBV infection can either be the route for transmission of HBV from the mother to the fetus or secondary to fetal infection by another route. To distinguish between these two possibilities, researchers have measured the gradient of placental infection between the maternal side and the fetal side of the placenta and concluded that in the majority of cases, transplacental infection is the mechanism for HBV intrauterine infection[41,42].

### 3.1.3. HBV infection at conception

Studies have also demonstrated that HBV-DNA exists in oocytes of infected females and sperms of HBV-infected males. Therefore, it is possible for the fetus to become infected with HBV at conception[42].

### 3.1.4. Intrauterine transmission of HBV

IV. Another possibility is the intrauterine transmission of HBV to the fetus, not from maternal blood but ascending from vaginal secretions of the mother that contain the virus[42].

### 3.2. Intrapartum transmission

Transmission of HBV to the infant at the time of birth is believed to be a result of exposure to maternal cervical secretions and maternal blood that contain the virus[43]. There is still some controversies regarding the effect of delivery mode on MTCT; in current obstetrical guidelines, the mother’s HBsAg positivity does not affect the planned mode of delivery irrespective of her HBeAg status or level of viremia. Some articles recommend cesarean section in case of high maternal HBV-DNA levels[44], whereas others believe that mode of delivery does not influence the rate of HBV transmission provided that all infants receive hepatitis B immune globulin (HBIG) and HBV vaccine at the recommended schedule[45]. A recent systematic review in 2008 on four randomized controlled trials involving 789 people concluded that cesarean section before labor or before ruptured membranes (elective cesarean section) appeared to be effective in preventing MTCT of HBV. However, the authors point out that the conclusions of this review must be considered with great caution due to high risk of bias in each included study (graded C)[46]. Randomized controlled trials of higher quality are required for assessing the effects of elective cesarean section in comparison to vaginal delivery for preventing MTCT of HBV.

### 3.3. Postpartum transmission

Although postpartum transmission of HBV is known to occur, it is thought to account for only a very small proportion of cases of perinatal transmission[47]. The exact mechanisms by which postpartum transmission occurs remain unclear as, to date, there is scant data in the literature regarding this issue, beyond passing references in the literature to postpartum transmission as a potential mode of perinatal transmission. However, potential mechanisms of postpartum transmission, all of which involve close contact of the infant with HBV-contaminated maternal secretions, may include: infant ingestion of maternally pre-masticated food, maternal kissing of the infant on the mouth and nosocomial infection due to poor hand hygiene practices amongst healthcare workers who are involved in the postpartum care of both mother and infant[48].

Although HBsAg, HBeAg and HBV DNA have been shown to be excreted from the colostrum and breast milk of mothers with chronic HBV infection[49-51], there is currently no evidence that breastfeeding increases the risk of mother-to-child transmission of hepatitis B. A recent systematic review of ten prospective studies, evaluating the role of breastfeeding in mother-to-child transmission of HBV, found that breastfeeding after adequate immunoprophylaxis did not contribute to postnatal transmission of HBV[52]. Furthermore, the World Health Organization has recommended that all infants should be breastfed for at least 4 months (but ideally, at least 6 months) as there is a considerable risk of morbidity and mortality from hepatitis B among infants who are not breastfed[53]. However, although breastfeeding per se is not thought to be a mechanism of postpartum transmission of HBV, breastfeeding in the presence of concomitant nipple pathology may potentially result in postpartum transmission of HBV due to contamination of the breast milk by serous exudates from the nipple lesions[48]. As a general rule, it is recommended to explain to mothers that they should take good care of their nipples while breast-feeding, ensuring proper latch-on and allowing the nipples to
4. Sex hormones support HBV infection in pregnancy

The liver also plays a crucial role in the metabolism of different hormones, including estrogens and progesterone. The normal course of pregnancy is bound to have a number of physiological changes and these changes may affect the normal course of chronic hepatitis B infection in infected women[55-57]. During pregnancy, successful fetal development is necessary by eliciting poor immune response against fetal antigens. Therefore, weak immunity of the mother might allow HBV viral replication and increase the chances of perinatal transmission of HBV infection in children.

Sex hormones such as androgens, estrogens and progesterone can directly interact with the cells of the immune system, thus impacting the development of immune responses. The female sex hormones estrogen and progesterone have been implicated as playing a role in modulating the local immune system and altering cytokines during pregnancy. Progesterone, a hormone associated with the maintenance of pregnancy, is immunosuppressive and decreases natural killer cell cytotoxicity, inhibiting nitric oxide and tumour necrosis factor production.

Progesterone that induced binding factor inhibits the activity of dendritic cells that generate pro-inflammatory responses and favors the induction of tolerogenic dendritic cells. It also controls the activity of natural killer cells and the differentiation of T cells into T helper cell type 2 (Th2) like clones (Figure 1). Therefore, progesterone mediates the immunological effects and induces the production of Th2 dominant cytokines like IL-3, IL-4, and IL-10[58] (Figure 1). The Th2 phenotype induced by progesterone is a prerequisite for the maintenance of pregnancy, which is associated with the susceptibility and the existing disease exacerbation[59,60]. The anti-inflammatory properties of progesterone prevent the development of Th1 responses that could result in fetal abortion[61].

In contrast to progesterone, estrogen is considered as a proinflammatory mediator. Estrogen has been shown to stimulate the production of the proinflammatory cytokine tumour necrosis factor[52,63], which is known to directly interact with the interferon (IFN)γ promoter[64], and further has been shown to enhance antigen-specific CD4+T cell responses[65]. The ability of estrogen to drive proinflammatory, Th1-associated immune responses induces higher concentrations of the proinflammatory cytokines, IL-6 and IFN-γ. Th1 responses are associated with protective immunity and favour disease resolution. Therefore, progesterone favors Th2 response which protects foetal development, and estrogen leads to Th1 response, which favors HBV disease resolution.

As pregnancy is a relatively immunosuppressed state, some of the chronic hepatitis B infected mothers may develop hepatitis flare or fulminant hepatic failure due to immune restoration during the peripartum period[66,67]. Generally, a significant increase in liver disease activity is being observed after delivery. Overt liver dysfunction was maximum as observed in 43% of mothers who were HBeAg positive within the first post-partum month[68]. These robust immune responses have cleared HBeAg in 12.5% of mothers during the first month of postpartum period[69].

5. Antivirals safety and concern

5.1. Prevention of MTCT

Prevention of MTCT is an essential step in reducing the global burden of chronic HBV[43]. In endemic areas, HBV infection occurs mainly during infancy and early childhood, with MTCT accounting for approximately half of the transmission routes of chronic HBV infections[70]. As discussed before, natal transmission accounts for most of MTCT, and providing immunoprophylaxis to newborns is an excellent way to block natal transmission. However, prenatal transmission might be responsible for the minority of MTCT.

5.1.1. Prevention of natal transmission

Immunoprophylaxis provided to newborns clearly reduces the incidence of perinatal HBV transmission. Vaccination of neonates of HBsAg-positive mothers is the most important and cost-effective step toward the eradication of chronic HBV infection[71]. A Cochrane systematic review in 2006 has shown that the relative risk of neonatal HBV infection in those who receive HBV vaccine alone is 0.28, while the addition of HBIG to this regimen further reduces the relative risk to 0.08 when compared with those who receive placebo or no intervention[72]. These data indicate that vaccination alone is insufficient to prevent transmission of HBV infection from HBeAg-positive mothers to their infants. Vaccination alone should only be considered in countries where HBIG is not available, in patients that cannot afford the cost of HBIG or in certain remote areas where a laboratory is not accessible for implementation of maternal HBsAg testing. The standard immunoprophylaxis regimen consists of both passive and active immunizations. HBV vaccine and HBIG are given at the same time at two different injection sites within 12 h of delivery. The infants then receive two additional doses of HBV vaccine at ages 1-2 months and 6-8 months[73-75]. As
noted before, even with the prompt administration of this standard immunoprophylaxis regimen, HBV infections in newborns still occur in some infants. Immunoprophylaxis is not 100% successful in blocking natal transmission either, and one putative mechanism of such failure is believed to be mutations in the S gene of HBV that cause conformational changes in the determinant of HBsAg (the major target for neutralizing antibodies against HBV). Although to date, the negative effect of such mutations on the success rate of immunoprophylaxis programs has not been proven, concern has been expressed that these variants might replicate in the presence of vaccine-induced anti-HBs or anti-HBs contained in HBIG. It has been proposed that enhanced surveillance to detect the emergence of these variants will be necessary for monitoring the effectiveness of current vaccination strategies[43].

5.1.2. Prevention of prenatal transmission

Levels of HBV DNA and alanine transaminase (ALT) are highly variable during entire course of pregnancy. In a few cases, HBV DNA levels seemed to rise in the third trimester or in the post-partum period, otherwise for entire duration of pregnancy the levels of HBV DNA remained stable. There are limited data available on anti-viral treatment during pregnancy which show symptomatically or asymptomatically HBV infection clearance during subsequent pregnancies and postpartum[76,77].

Because of the clear correlation between the risk of intrauterine transmission of HBV and the level of maternal viremia, a growing number of trials have investigated the role of adding additional antiviral therapy with a nucleoside analogue late in pregnancy to standard immunization and prophylaxis to decrease maternal viral load and MTCT. The oral nucleoside analogs indicated for the management of HBV infections are all listed as either a category B or a category C (Table 1) agent by the US Food and drug Administration. Lamivudine, adefovir and entecavir are designated category C drugs; telbivudine and tenofovir are category B drugs. The use of antivirals from the first trimester showed more birth defects than their use in third trimester. Usage of recent antivirals in the first trimester, including emtricitabine, tenofovir, lamivudine, telbivudine, and adefovir showed more than 1.5 fold increase in overall birth defects[78]. Pregnant women with a low HBV viral load do not require immediate treatment, because due to the passive immunization and active HBV vaccination of the newborn, chances of acquiring infection due to perinatal transmission are negligible. Treatment of the mother can, therefore, be postponed until after the birth. However, with high HBV viral load (>10^6 copies/mL in serum), strategy for treating with antivirals during the last trimester of pregnancy is being considered[79]. Antiviral therapy was also used in pregnant woman with acute exacerbation of hepatitis B, as this was quite effective in reducing possible HBV-associated hepatitis flares or reactivation and made a difference to maternal morbidity and mortality before hepatic de-compensation[78,80]. However, vertical transmission has been reported even with the treatment of hepatitis B during the pregnancy and when there was an undetectable viral load at delivery[79]. In antivirals, lamivudine was the first drug that was used to diminish viral load and considered effective in the third trimester of pregnancy and resulted in reduced risk of chronic hepatitis B in the child[78,81,82]. Oral dose of 150 mg of lamivudine every day during the last month of pregnancy reduced serum HBV DNA concentration and normalized ALT levels till the time of delivery. In the lamivudine-treated group, only 12.5% infants were tested positive for HBsAg in comparison to 28% untreated historical control subjects. Therefore, lamivudine therapy was considered effective in reducing HBV transmission from highly viraemic mothers to their infants who received passive/active immunization. Despite the fact that lamivudine therapy leads to suppression of the HBV DNA to undetectable levels in the mother, there is a case report of a newborn with raised ALT levels and positive for HBV DNA at birth, followed by developing chronic hepatitis B virus infection[83]. A meta-analysis of ten studies concluded that the addition of lamivudine therapy in late pregnancy to the standard HBV vaccination and HBIG prophylaxis significantly reduced MTCT[84]. Considering the above points, lamivudine prophylaxis is still a controversial issue; however, it might be used in a subset of pregnant women with very high levels of HBV-DNA (i.e., HBV-DNA >8-9 log 10 copies/mL). Recently, telbivudine was evaluated for its efficacy and safety in the third trimester of pregnant women in one of the clinical trials and also compared with lamivudine[78,83]. Both antivirals showed reduction in HBV DNA levels in mothers from log 8 to log 2. Newborns were given hepatitis B vaccination as well as immunoglobulin within 24 h of birth and completed vaccine schedule. After one year of birth, 18% of children in lamivudine group showed HBsAg positivity, however, in telbivudine group only 2% children showed HBsAg positivity. Therfore, telbivudine was considered to be better antiviral than lamivudine[78]. Most of the antiviral data support lamivudine and tenofovir usage in the pregnancy than adefovir and entecavir, as safety of entecavir is questionable. The global recommendations are to use tenofovir, lamivudine, and telbivudine during pregnancy and substantial registry evidence positively supports the use of tenofovir, which is a potent inhibitor of HBV[83]. However, in the case of lamivudine or telbivudine antiviral therapy, genotypic resistance should be assessed during treatment[85].

Table 1

| Drugs          | Pregnancy category |
|----------------|--------------------|
| IFN-α          | C                  |
| Peg-IFN-α      | C                  |
| Adefovir       | C                  |
| Entecavir      | C                  |
| Lamivudine     | C                  |
| Telbivudine    | B                  |
| Tenofovir      | B                  |

Category B drugs: No teratogenic/embryogenic risk in animal studies and no controlled human studies available or risk in animal studies, but controlled human studies refute these; Category C drugs: Teratogenic/embryocidal effects in animals, and no controlled studies in humans.

5.2. Antiviral therapy

Antiviral therapy is recommended to continue in postpartum period but the safety of anti-viral therapy during lactation period is
a concern. Though HBsAg has been detected in the breast milk, globally breast feeding has not been contraindicated in HBsAg positive mothers[86]. There are not many studies discussing the effects of antiviral therapy during lactation period[87,88], however, a study on lamivudine treated pregnant women showed that infant received only 2% of recommended antiviral dose through breast milk and the tenofovir treated HIV group showed only 0.03% release of recommended dose in breast milk[89].

Antiviral therapy might not prevent perinatal transmission of HBV infection in every newborn, therefore, use of antivirals during pregnancy need to be individualized, and as the evaluation and management of abnormal liver tests in the pregnant women is challenging, importance of understanding case by case natural history of chronic HBV infection in the peri-partum period is extremely vital.

After birth, HBsAg positivity in children varies. In India, children below 15 years old have 1.3%-12.7% HBsAg positivity, whereas in other countries it ranges from 0% to 7.8%[8-10]. Ultimately children after perenatal transmission with detectable HBV DNA levels are being treated with antivirals and interferon[90], however, the success rate and adverse effects need to be determined.

6. Management algorithm for prevention of prenatal transmission

In devising this algorithm (Figure 2), which is adapted from an algorithm by Yogeswaran and Fung[91], it should again be noted that in HBsAg-positive pregnant women with high HBV DNA viral load, the use of lamivudine in the third trimester of pregnancy, followed by passive and active immunization of the newborns, has been proven to be effective in preventing transmission of HBV to the fetus and is currently considered to be safe for both the mother and

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Figure 2. Management algorithm for prevention of prenatal transmission of HBV infection[91].

*Appropriate counseling regarding treatment, treatment duration, potential side effects, monitoring on treatment and cessation of therapy if breastfeeding is chosen.
the developing fetus. Administration of HBIG during pregnancy is expensive and there is currently insufficient evidence to justify its widespread use.

7. Conclusion

Numerous studies on HBV infection, its sequelae, and the various means of prevention have been published in the past three decades. Yet even the latest studies have found areas of deficient or even erroneous knowledge on HBV infection. Social stigma can result from poor knowledge on HBV infection, as is the case in Mainland India. In India, HBV carriers face social discrimination, affecting both their life and work as many employers and universities refuse to accept those who were tested positive from the pre-employment and pre-enrolment medical checkup. On the other hand, appropriate public education could reduce the stigma attached to HBV carriers, as shown in the United States that higher levels of knowledge regarding HBV were associated with lower degrees of stigma[92]. More studies on the control of HBV infection through enhanced public health education programs as an adjunct to any ongoing immunization program in endemic areas are warranted. Urgent strategies are required to address the global health burden that chronic HBV infection imposes. It is imperative for nations to formulate and implement consistent population-based screening and universal vaccination programs. Although immune-prophylaxis has been extremely successful and is the mainstay of therapy in pregnant women with low HBV DNA viral loads, there is a growing body of evidence strongly favoring the adjunct use of antiviral therapy during pregnancy in order to reduce the risk of perinatal transmission, especially as positive data accumulates regarding the safety profile and efficacy of medications such as lamivudine, telbivudine and tenofovir. However, there is a clear need for close monitoring of both pregnant women with hepatitis B infection and their infants, both during and after pregnancy.

Conflict of interest statement

We declare that we have no conflict of interest.

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