MINI REVIEW

Hepatitis B virus infection and pregnancy

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Summary  Pregnancy only mildly affects that natural progression of acute and chronic infection by the hepatitis B virus (HBV) but it does bring to light three important questions. Mother to child (vertical) transmission risk is best prevented by mandatory HBs antigen testing in all pregnant women in their second trimester and by systemic serovaccination of newborns of infected mothers. In mothers with high viral load, vertical infection in utero could be prevented by lamivudine, telbivudine or tenofovir treatment. Invasive obstetric or gynecological procedures (such as amniocentesis, forceps, etc.) do not seem to increase the risk of vertical infection. Breastfeeding is not contraindicated in maternal HBV infection after serovaccination of the newborn. This holds true for mothers on active treatment with tenofovir which is not absorbed into breast milk. When it comes to managing active antiviral treatment, in absence of virosuppression with lamivudine, tenofovir remains a logical step-up treatment; in absence of virosuppression with adefovir, tenofovir also remains a logical step-up choice as do tenofovir/emtricitabine combinations or lamivudine in absence of preexisting resistance which may have been induced during combination treatment of adefovir and lamivudine. In cases of effective virosuppression with treatment by analogues, lamivudine should be continued and entecavir should eventually be replaced by lamivudine, telbivudine or tenofovir; adefovir should be replaced by tenofovir or lamivudine in absence of resistance (which would require tenofovir therapy) or adefovir which would restrict lamivudine therapy.

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Hepatitis B virus (HBV) infection is one of the most common infections in the world, to which we attribute more than 350 million chronic infections, defined as chronic positive HBs antigen by serology [1]. This chronic infection burden is responsible for 1 millions deaths per year, largely linked to hepatocellular carcinoma (HCC) which are mostly secondary to HBV cirrhosis [2]. This reality has changed little in recent history in spite of the availability of an extremely effective vaccine for over 20 years [3]. This is closely linked to vaccination politics in endemic areas where more than 10% of the population have or had chronic infections, where few or no effective preventive policies exist. This also explains the persistence of chronic infection in these areas, largely due to vertical (maternofetal) transmission. This justifies serologic testing of all pregnant women to prevent the transmission with the serovaccination in newborns of infected mothers and systemic vaccination of newborns to limit the

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spread of the virus in others. Viral load suppression near the end of pregnancy to limit in utero spread is possible and brings to light the important question of end-of-pregnancy prophylactic treatment of high viral load mothers by using immunoglobulins or analogs.

Baseline knowledge

HBV is transmitted parenterally (IDVU, exposure to blood and blood products), sexually (leading method of infection in developed countries) and vertically (mostly prevented in developed countries but remains the cause of spread in endemic regions). Risks include: (1) fulminant hepatitis, which is also seen in newborns who have not had the benefit of prophylactic vaccination, as was demonstrated in the first months of mandatory declaration of acute HBV [4] and (2) development of chronic hepatitis. Defined as the continued positivity of the HBs antigen for more than 6 months without anti-HBc IgMs, chronic infection occurs in about 5–10% of those with acute infection in adults and children older than 5 years, in 25–50% of children between 1 and 5 years, and 90–95% of perinatal infections [5–7]. Twenty percent (20%) of chronic infections will evolve into liver cirrhosis [8] with both its neoplastic and nonneoplastic complications [8,9].

In endemic regions, most infections occur at birth or at a very young age [10—12]. These infections remain asymptomatic and the risk of chronic evolution is very high. In south-east Asia, in the east or in pacific regions, 30–50% of chronic infections in children are of vertical etiology linked to a high viral load in mothers. Paradoxically, in Africa, South America and in the Middle East, where viral loads seem to be less, vertical transmission represents only 10–20% of chronic infections in children. In intermediate and low endemic zones, 10–20% of infections are linked to vertical transmission [12].

Consequences of pregnancy on HBV infection

Acute hepatitis can occur throughout all pregnancies, at any stage, and should be discussed with all pregnant women with elevated transaminases and positive anti-HBc IgMs which confirm recent infection. Over the first weeks of pregnancy, acute HBV infection can be the cause of spontaneous abortion but generally resolves without severe consequence for mother or child [13]. Contrarily, the onset of acute HBV infection at the end of pregnancy can cause vertical infection in utero [14].

Pregnancy has little effect of chronic HBV infection [13]. Immunologic changes in pregnancy and in the postpartum phase can lead to changes in HBV manifestation including an increased viral load in the second and third trimesters, reactivation of the virus [15] to potentially the fulminant stage or seroconversion which is favored by the return to baseline of the immune system in the long-term after delivery. Above all, chronic hepatitis can be at the origin of vertical transmission in utero, in cases of high-viral load [16].

Vertical transmission

Vertical transmission is the main reason for the continued endemic infection rates, at least in Asia. The four following methods of vertical transmission are noted.

Transmission in utero

In utero HBV infection explains the failure of passive and active immunoprophylaxis methods and largely depends on maternal HBV load [16]. It can be linked to hematogenic spread to placental capillary endothelial cells (likely the principal method) or by cell to cell transfer: the placental HBV infection load decreases proportionally from the maternal cells to the fetal cells, and a link between in-utero HBV infection and villous capillary endothelial cell infection was recently reported [14]. Outside of Asia, this route of transmission is unusual [14,16].

Transmission by amniocentesis or method of delivery

Two studies including 68 women suggest that amniocentesis does not increase the risk of vertical transmission and that, after amniocentesis, all properly immunized children at birth are protected from HBV infection [17]. The method of delivery (C-section, vaginal with and without forceps) does not modify the incidence of failure of immunoprophylaxis, of about 7% in 300 Chinese children [18].

Neonatal transmission

Vertical HBV contamination occurs generally during delivery, either by blood mixture during labor, either by contact of the child with infected bodily fluids. HBs antigen is detected in 50% of cases in cord blood and in 95% of gastric fluids in children born of infected mothers. In mothers with increased HBV replication detected by hybridization (cutoff at 700,000 copies/mL), the transmission risk to the newborn is 90% and the chronic infection risk is 80–90% [19]. Infection by a pre-C mutant, associated with a lower viral load, reduced the risk of chronic infection. In absence of detectable HBV DNA in the mother, infection risk is between 10–30% but curiously, it is in these cases that acute or fulminant hepatitis infections are observed in the newborn. If the onset of acute HBV infection is in the third trimester of pregnancy. The actively undergoing viral replication at time of delivery explains that it is transmitted in 65–100% of cases. Due to the long incubation time of HBV (6 weeks to 6 months), acute hepatitis in the postpartum period can also cause infection which is likely attributable to the mothers’ viremia at time of delivery in the absence of clinical manifestations [14].

Postnatal transmission

HBV is only detectable in breast milk by PCR and therefore makes of breastfeeding a theoretical method of transmission, either by ingestion of the virus or by contact with skin lesions on the mother's breast. Infection rates were no
different between children of breastfeeding mothers (53%) and bottle fed (60%), this data dating to times were vaccination was not available. If newborns are properly serovaccinated, there is no indication against breastfeeding [19].

Vertical transmission prevention

Vaccination and serovaccination

If passive immunization with anti-HBs immunoglobulins (HBIG) has demonstrated its effectiveness in the perinatal pediatric infection rates, it holds that it should be used with active immunization by vaccination in order to keep with current best practices [20]. The combination of HBIG and vaccination has demonstrated effectiveness in HBV prevention since 1982 [21]. In endemic areas, the WHO recommends systemic newborn vaccination regardless of maternal HBV status to reduce the risks of vertical infection [10]. Moreover, in mothers with positive HBe antigen, it is recommended to administer an HBIG injection once the positive HBs status is confirmed. In moderate or mildly endemic areas, testing for the HBs antigen should be systematically done in all pregnant women. In cases where HBs antigen is positive, a specific serovaccination must be administered to the newborn ideally in the first 12 hours of life [22] which consists of a first IM injection of HBV vaccine and, at another IM site, an HGIB injection (consisting of 200 IU when mother tests positive for HBe antigen and 100 IU when mother is HBe negative). Repeat vaccinations should be done at 1 month (with a second dose of HBIG if mother is HBe Ag-positive in some countries) and a 6 months for complete vaccination. In areas where HBIG is not available, vaccination should take place following the same schedule.

In France, the second injection of HIBG is not recommended and a serology has to be performed from one to four months after the last injection of vaccine to check the efficacy of serovaccination. In premature newborns (lower than 32 weeks of pregnancy or less than 2 kg as birth weight), four vaccine injections are recommended instead of three.

Adherence to recommendations

The best practice guidelines which recommend testing of HBV status in pregnant women and of systemic serovaccination of children born to infected mothers are insufficiently respected in France. A recent study demonstrates that only 80% of pregnant women benefit from HBV serology and that complete serovaccination is achieved in only 60% of children born to HBV positive women [23]. Two recent studies, one Swiss and one English, suggest that 99% of pregnant women are evaluated (8% during labor and delivery) and that 95% of children receive serovaccination although complete vaccination including two follow-up injections is achieved in only 53% of children, and only 12% receive immunization in the recommended timeframe [24,25].

Effectiveness of serovaccination

The superiority of serovaccination over vaccination alone or with passive immunity is unarguable due to the fact the serovaccination prevents vertical transmission in 89—100% of cases. The risk of transmission and of failure of serovaccination depends largely on viral multiplication levels. Serovaccination works to reduce transmission in 85—92% of newborns of mothers with active viral replication and in 100% of newborns of mothers with nonreplication HBV [26,27]. Eighty percent of children will develop an adequate anti-HBs response with a protective titer over 10 mIU/mL [28]. Antibody concentrations then drop-off over time in such a way that 80% of children will maintain effective serovaccination 5—14 years later [29]. It follows that serovaccinated children should be called back for booster vaccination likely after the age of 15 years.

The effectiveness of serovaccination or at least of systemic vaccination of children born of HBV infected mothers in addition to vaccination of all children and adolescents, as was realized in Singapore and Taiwan, yields:

- a major reduction in HBs antigen carrier rates between 1989 (more than 10% of citizens) and 1993 (less than 2% of citizens) [30] (Fig. 1);
- a significant reduction of chronic hepatitis cases in these countries [31];
- a reduction in mortality, mostly by reduction of HCC rate both in adults and in children [32,33] (Fig. 2).
Thus, neonatal HBV vaccination is the first documented vaccination to dramatically reduce the risk of liver cancer. Lastly, many studies have demonstrated the economic benefit of systemic HBV vaccination.

**Prevention of in utero transmission**

Failures to serovaccinate are less attributable to failure of preventive public policy and more attributable to in utero transmission, mostly observed in Asia women with high viral replication loads. Repeated administration of HBIG during the last 3 months of pregnancy reduces the risk of in-utero transmission; just as the use of nucleoside analogs such as lamivudine or telbivudine and nucleotide analogs such as tenofovir and can thus be used during pregnancy. Administered at a dose of 150 mg in the last weeks of pregnancy in association with a preexisting neonatal serovaccination, lamivudine reduces but does not eliminate the risk of perinatal transmission. In a study comparing serovaccination, lamivudine reduces but does not eliminate the in-utero transmission of HBV by systematic and mandatory HBs antigen prophylaxis in utero. It seems logical to choose tenofovir as primary treatment as it is both more effective and induces less resistance at 2 years when compared to lamivudine or telbivudine. The only unanswered question in these women with no indication for treatment, and who are immune tolerant, is that of duration of treatment. Logic maintains that treatment should continue until 6 months after childbirth, at least for mothers who are breastfeeding and are treated with tenofovir. The major risk is reactivation at the end of treatment or induced resistance. If a pregnant female is not treated and has a low viral load (inferior to \(7 \log \text{IU/mL}\)), serovaccination is sufficient for the prevention of vertical transmission and treatment with analogs appears to be fruitless in absence of hepatic indicators (inflammatory activity, fibrosis and high viral load according to EASL guidelines; transaminase levels appear to be a poor treatment criteria during pregnancy).

**Untreated pregnant mothers with elevated viremia**

Untreated pregnant mothers with elevated viremia (greater than \(7 \log \text{IU/mL}\)) will probably require vertical transmission prevention in utero. It is logical to choose tenofovir as primary treatment as it is both more effective and induces less resistance at 2 years when compared to lamivudine or telbivudine. The only unanswered question in these women with no indication for treatment, and who are immune tolerant, is that of duration of treatment. Logic maintains that treatment should continue until 6 months after childbirth, at least for mothers who are breastfeeding and are treated with tenofovir. The major risk is reactivation at the end of treatment or induced resistance. If a pregnant female is not treated and has a low viral load (inferior to \(7 \log \text{IU/mL}\)), serovaccination is sufficient for the prevention of vertical transmission and treatment with analogs appears to be fruitless in absence of hepatic indicators (inflammatory activity, fibrosis and high viral load according to EASL guidelines; transaminase levels appear to be a poor treatment criteria during pregnancy).

**Breastfeeding**

When the mother decides to breastfeed her infant, breastfeeding is not a contraindication in chronic HBV infection as long as serovaccination has been performed. Tenofovir appears to be the best therapeutic modality not only in term of antiviral effect and anti-resistance profile but moreover its particular characteristic of not being secreted in breast milk. It has also been demonstrated to induce no increased risk of renal failure, osteomalacia of the newborn or other pathologies (e.g. mitochondriopathies).

In summary, it is necessary to reduce vertical transmission of the HBV by systematic and mandatory HBs antigen testing in all pregnant women in addition to systematic serovaccination in newborns of infected mothers. In mothers with elevated viral replication rates, which also justifies repeat measurements throughout pregnancy, prophylaxis against in-utero transmission by lamivudine or tenofovir should be considered in the last weeks of pregnancy in addition to serovaccination in the corresponding newborns.

**Disclosure of interest**

Board Member: BMS, Boehringer Ingelheim, Tibotec/Janssen Cilag, Gilead, Roche, Merck/Schering-Plough, Abbott;
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