

Paths to Eliminate Maternal-Fetal Hepatitis B Transmission: Focusing on the Peri-Partum and Neonatal Phases

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Childhood HBV infection is associated with chronic infection in 80 - 90% of those who acquired the virus at a very young age. The disease has many sequelae whereby 12 - 20% of the chronic cases progress towards liver cirrhosis in the next few decades, and among them, there is 6 - 15% 5-year risk of hepatocellular carcinoma and 20% risk of hepatic decompensation [1]. In the last millennium, infants born to hepatitis B positive mothers were very susceptible to the virus, as a result of intra-partum and intra-utero maternal-fetal transmission routes. Many observational studies showed peri-partum was the critical period where viral transmissions took place. In addition, pregnant women with a few other risk factors were at increased odds of infecting their newborns. Some estimated the transmission rate to be as high as 90 - 95% in the absence of any immuno-prophylaxis [2]. Maternal hepatitis B e-antigen positivity and high HBV DNA levels were predictors of HBV surface antigen positivity and viremic status in the first year of their newborns. Timely intervention was clearly needed. Thus, in many parts of the world, universal hepatitis B screening program has become the standard of care in early pregnancy. The universal HBV vaccination program has also become parts and parcels of neonatal cares around the world, offering perinatal immuno-prophylaxis and HBV vaccinations to millions of infants born to mothers with positive hepatitis B surface antigens. These proactive measures led to a noticeable drop in the incidence of childhood hepatitis B in areas where HBV was endemic.

In the recent decades, the use of anti-viral nucleos(t)ide analogues in pregnancy was studied. Some of the earliest safety data came from women living with human immunodeficiency virus (HIV) who were on an anti-HIV nucleoside analogue. Lamivudine was trialed in an HBV population at a double-blind and placebo-controlled study. In this study, lamivudine was randomized to 150 women between gestational age 26 to 30 weeks. The result showed lamivudine was safe to pregnant mothers and infants [3]; miscarriage rate, post-partum hemorrhage, birth defects were not significantly different between treatment and placebo arms. In a non-randomized prospective study, telbivudine given at 20 to 32 weeks was well tolerated in pregnancy and newborns followed up to 6 months post partum experienced no adverse events [4]. More prospective studies and meta-analyses supported the use of a nucleoside analogue in the late second to third trimesters, as they significantly suppressed HBV DNA level at the time of delivery, and newborns had a much lower likelihood of HBV infection, manifested by positive or negative surface antigens (HBsAg) at birth [5].

The use of hepatitis B immunoglobulin was also extensively studied in this special population. In a prospective study, newborns were administered hepatitis B immunoglobulin and first dose of HBV vaccination within 12 hours of their births. Despite this, some newborns (7 to 28%) still became HBsAg and DNA positive at birth or at 6 months. These infants were infected with the same viral strain as their mothers, suggesting maternal-fetal transmission were taking place and the risk was only higher if the mothers had a high HBV DNA level above 7log IU/ml [6].

In HBV endemic regions where maternal-child is the main transmission route, it is cost-effective to combine immuno-prophylaxis and an anti-viral agent in order to prevent vertical transmissions. An anti-viral agent is given a few months before the estimated due date to suppress maternal HBV DNA viral load at the time of delivery. The dual strategies had decreased infant HBV infection rates to less than 1% from greater than 7 to 10%. Nucleos(t)ide analogue use in the late second and third trimesters in those with high viral loads was recommended by the European Association for the Study of the Liver and American Association of the Study of the Liver Disease. The recommendations were based on many low quality studies and meta-analysis derived from them.

The recommendations were subsequently refined by more high quality studies. There was a randomized controlled study from 2016, which selected 200 e-antigen positive pregnant women, all had DNA level greater than 200,000 IU/ml, and were randomized to daily tenofovir disoproxil fumarate (TDF) or regular care at 30 to 34 weeks during pregnancy to post partum week 4 [7]. Mothers and newborns were followed till post partum week 28. All infants were given immunoprophylaxis (HBIG plus first dose of HBV vaccination within 12 hours of the birth). In the intention-to-treat analysis, newborn HBV surface antigen positivity or HBV viremic status at 28 weeks was significantly lower at 5% in the TDF arm versus 18% in the control, correlating to a markedly suppressed maternal DNA level in the TDF arm at the time of delivery. As expected, maternal and infant safety outcomes were similar in TDF users and non-user. The other important finding was the incidence of post-partum HBV flare following TDF withdrawal at week 4, and that there were no adverse events or clinically significant hepatitis B flares reported by the study.

Between 2013 and 2015, a double blind randomized study was conducted in Thailand by recruiting three hundred and thirty one pregnant women who were HBV e-antigen positive and had high DNA levels. One hundred and sixty-eight of them were randomized to daily TDF or placebo from 28 weeks till post partum week 8 [8]. All newborns received HBIG and HBV vaccination immediately at birth. The study was published in 2018. Approximately 87-90% of the women had DNA levels > 200,000 IU/ml at baseline. While the trend persisted in the placebo group, 88% of TDF group lowered DNA level to less than 200,000 IU/ml at the time of the delivery. In both the intention-to-treat and per-protocol analyses, the rate of HBV infection in the newborns were surprisingly low at 2% in the placebo arm at 6 months which was not statistically different from 0% in the TDF arm. The study was the first to show TDF in combination to HBIG/vaccination was non-superior to HBIG/vaccination alone in reducing maternal-fetal HBV transmission. The authors concluded that TDF was highly safe to use in the late second to third trimesters; cesarean section rate, post partum hemorrhage, pre-mature birth rate, apgar scores, birth weight and birth defect rate were not affected by TDF use. Although the authors found a lack of additive benefit of TDF use unlike the findings by others, they pointed to a relatively small sample size of this study, and in this trial the median time of immune-prophylaxis was at 1.3 to 1.4 hours post delivery, a much more expedited version than all the other trials. It is unclear whether it may have contributed to the results. More HBV infection in the newborns may have been otherwise prevented by this early administration of HBIG/HBV vaccination. In the real world settings at present, few centers would be following the early protocol of immunoprophylaxis within 2 hours of births. More RCTs investigating the timing of immune-prophylaxis are needed to verify these new findings.

In conclusion, based on the literature to date, it is both safe and efficacious to give a nucleos(t)ide analogue such as lamivudine, telbivudine or tenofovir in late-second and third trimesters. Infants born to HBV DNA mothers should all receive immuno-prophylaxis in the form of HBIG and HBV vaccination shortly after birth, particularly in cases where HBV DNA remained persistently high at the time of deliveries. Whether an expedited HBIG or vaccination should be given in these particular situations are unclear but worth investigating. Going forward, there must be a joint decision making between an obstetrician/neonatologist and a hepatologist to optimize the management of HBV in pregnancy based on the changing guidelines and new literature evidence.

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