Tenofovir for Prevention of Mother-to-Child Transmission of Hepatitis B

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SUMMARY

In this trial, 200 mothers, who were positive for hepatitis-B e antigen (HBeAg) and who had hepatitis-B virus (HBV) DNA level >200,000 IU/mL, were randomly assigned to receive usual care without antiviral therapy or to receive tenofovir (TDF) at an oral dose of 300 mg/d from 30 to 32 weeks of gestation until postpartum week 4; the participants were followed until postpartum week 28. All the infants received immunoprophylaxis. The primary outcomes were the rates of mother-to-child transmission and birth defects. The secondary outcomes were the safety of TDF, the percentage of mothers with an HBV DNA level of <200,000 IU/mL at delivery, and loss or seroconversion of HBeAg or hepatitis B surface antigen at postpartum week 28. At delivery, 68% of the mothers in the TDF group (66 of 97 women), as compared with 2% in the control group (2 of 100), had an HBV DNA level <200,000 IU/mL. At postpartum week 28, the rate of mother-to-child transmission was significantly lower in the TDF group than in the control group, both in the intention-to-treat analysis (5% *vs*. 18%, *P*=0.007) and the per-protocol analysis (0 *vs*. 7%, *P*=0.01). The maternal and infant safety profiles were similar in the TDF group and the control group, including birth defect rates (2% *vs.* 1%, *P*=1.00), although more mothers in the TDF group had an increase in the creatine kinase level. After the discontinuation of TDF, alanine aminotransferase elevations above the normal range occurred more frequently in mothers in the TDF group than in those in the control group (45% *vs*. 30%, *P*=0.03). The authors concluded that in HBeAg-positive mothers with an HBV DNA level >200,000 IU/mL during the third trimester, the rate of mother-to-child transmission was lower among those who received TDF therapy than among those who received usual care without antiviral therapy.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Perinatal transmission of Hepatitis B infection is associated with unpleasant consequences for individuals as well as the society – the former because transmission from mothers with active viral replication is associated with high probability of chronicity in the affected offspring, and the latter because it contributes to the pool of chronic carriers in the community. The impact of perinatal transmission has been significantly mitigated by the strategy of combined passive (immunoglobulin) and active (vaccination) immunization [1]. However, it is reported that these measures are unsuccessful in cases with high load of actively replicating viruses (HBeAg positive women with HBV DNA >1 million copies/mL) [2,3]. In such situations, there is emerging data that antiviral agents such as telbivudine administered to pregnant women may be efficacious [4], well tolerated [5] as well as cost-effective [6]. Researchers have also tried other antiviral agents including tenofovir [7]; however robust evidence is lacking. Pan, *et al*. [8] sought to address this gap through a randomized controlled trial (RCT) comparing tenofovir (Intervention) *vs* usual care (Comparison) for preventing perinatal transmission of Hepatitis B (Outcome) from mothers with high viral load (Population). ***Table* I** presents the trial outline.

Critical appraisal: The RCT was well designed and conducted as planned. ***Table* II** presents a summary of critical appraisal of methodological characteristics using the Cochrane Risk of Bias tool [9]. Overall, the trial had moderate risk-of-bias. The trial included several refinements worthy of mention. Follow-up till 28 weeks postpartum is fairly standard in such trials. The investigators attempted to measure adherence to therapy by counting pills at follow-up visits (although the data are not presented). Follow-up visits were fairly frequent (every 4 weeks before delivery) and thereafter at 4, 12, 24 and 28 weeks postpartum.

The investigators also attempted to monitor development of antiviral resistance by genome sequencing of HBV in case of breakthrough or early discontinuation of treatment. Various terminologies

TABLE I OUTLINE OF THE TRIAL

Study design	Randomized controlled trial
Study setting	Five academic institutions located in five geographic regions in China
Study duration	16 consecutive months
Sample size	*A priori* sample size calculation was made assuming a baseline perinatal transmission rate of 20%, alpha error 5% and beta error 15%, and expected effect size of 90% reduction. The calculated sample size of 200 was achieved.
Inclusion criteria	Pregnant women (20-35y) with chronic hepatitis B and evidence of active viral replication (HBe Ag positive and HBV DNA >200,000 IU/mL).
Exclusion criteria	HIV positive status, previous adverse outcomes during pregnancy/delivery, prior therapy for HBV infection, hepatic decompensation, previous renal dysfunction, current kidney dysfunction (measured objectively), anemia, neutropenia, evidence of hepatitis (defined and measured objectively), fetal anomalies, intake of steroids, NSAIDs, nephrotoxic drugs, and chronic hepatitis B in the biologic father.
Intervention and Comparison groups	Intervention (Tenofovir group): Oral tenofovir 300 mg daily from 30-32 weeks gestation until 4 weeks postpartum. Comparison (Usual care group): No placebo was used.
Outcomes	*Primary outcomes:* • Vertical transmission rate (defined as infants with detectable HBV DNA *ie* >20 IU/mL or HBsAg positive at 28 postpartum weeks) • Birth defects in infants (defined in detail) *Secondary outcomes:* • Maternal HBV DNA <200,000 IU/mL at delivery • Mothers losing HBeAg or HBsAg at 28 weeks postpartum • Adverse events in mothers • Safety events in mother-infant dyads
Statistical analysis	Data were analyzed by intention-to-treat (ITT) wherein all enrolled participants who received the assigned treatment were included in analysis. Those who dropped out/ did not follow-up were assumed to have treatment failure. Per protocol analysis was also done. Investigators undertook appropriate statistical tests.
Main results (tenofovir *vs* no tenofovir)	*Primary outcomes* • Vertical transmission rate: 5/97 *vs* 18/100 • Birth defects in infants: 2/95 *vs* 1/88 *Secondary outcomes* • Maternal HBV DNA <200,000 IU/mL at delivery: 66/97 *vs* 2/100 • Mothers losing HBeAg or HBsAg at 28 weeks postpartum: 1/97 *vs* 4/100 • Adverse events in mothers: 61/97 *vs* 47/100 (for any event) and 1/97 *vs* 0/100 (for grade 3 or 4 event)

associated with the trial were strictly defined and objective criteria used where feasible. The authors also conducted several post hoc analyses and presented them in Supplementary tables. Data were analyzed by intention-to-treat, although the principle that all randomized participants should be included in the analysis (irrespective of whether or not they receive the intended treatment) was not strictly followed. The investigators did not pursue statistical modelling with best-case and worst-case scenarios.

Extendibility: India qualifies as a low intermediate endemicity country based on chronic HBV infection prevalence in the general population ranging from 2-4% [10,11]. Current data indicate that less than 1-1.5% pregnant women are chronic carriers [12-14]. The precise contribution of perinatal/vertical transmission the pool of chronic carriers in India is unclear. This is in contrast to China which is regarded as a highly endemic country with >8% chronic carrier rate [10], and 5-10% of the chronic carrier pool is derived by vertical transmission [15]. For these reasons, the decision to treat eligible pregnant women with antiviral agents, in our setting has to be individualized rather than empiric [16].

Conclusion: This well-designed multicentric randomized trial suggests that in pregnant women with high probability of transmitting hepatitis B vertically,

TABLE II METHODOLOGICAL APPRAISAL OF THE TRIAL

Similarity of groups at baseline	Maternal age, parity, baseline HBV DNA and ALT levels were comparable between groups. Infant gestation, mode of delivery, anthropometric measurements, and 1 minute Apgar score, were also comparable.
Sequence generation	A random number table was used and participants were randomized in blocks. No other details are available.
Allocation concealment	There was no allocation concealment procedure.
Blinding	This was an open label trial where neither the participants, not outcome assessors were blinded.
Incomplete outcome data	There is no evidence of incomplete reporting for short-term/immediate outcomes.
Selective outcome reporting	Almost all possible outcomes relevant to the PICO question have been presented.
Other sources of bias	The trial was funded by the manufacturer of tenofovir, but the authors stated that the funding agency/sponsor did not influence the trial or its reporting.
Overall assessment	Moderate risk of bias.

tenofovir initiated during the third trimester and continued beyond delivery could be a useful intervention to reduce perinatal transmission.

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Obstetrician's Viewpoint

Perinatal Hepatitis B infection has an 85-95% risk of chronic infection and 25-30% lifetime risk of serious complications or fatal liver disease [1]. Active and

passive immunoprophylaxis using Hepatitis B immunoglobulin and Hepatitis B vaccine offers 95% - 97% protection from perinatal infection. True immunization failure is around 3% and further increases to 7-9% in HBe antigen (HBeAg) positive mothers and those with a high viral load (10^8copies/mL) [2].

In their study, Pan, *et al.* [3] included 200 HBeAg positive women with high viral load (>200,000 IU/mL). The maternal to child transmission was significantly less in the tenofovir (TDF) group as compared to the control group in both intention-to-treat analysis (5% *vs* 18%) and per protocol analysis (0% *vs* 7%) at 28 weeks postpartum and fetal safety profile was similar in both groups.

Factors to consider drug therapy for routine use in prevention of mother-to-child transmission include risk of postpartum flares on stopping treatment, drug resistance and lack of long term safety data. In the present study, there was a significant elevation of alanine aminotransferase levels after discontinuation of TDF and 89% had a viral rebound on stopping treatment at 4 weeks postpartum. Drug resistance is reported to be low with TDF as compared to Lamuvidine, and in this trial all five women with viral rebound showed no genotypic mutation.

The birth defects rate is 2.7% with Tenofovir; however, the defects have only been identified at birth and there is a short follow-up. Tenofovir was given to women in the third trimester; hence teratogenic potential of the drug cannot be interpreted in the study. One stillbirth and neonatal death was reported in the TDF group as compared to none in the controls but the reasons cited were not linked to TDF. Limited data is available on maternal side effects like bone remodelling and osteoporosis; maternal creatinine kinase levels were elevated in this study and the result was interpreted as clinically non-significant. Another area of contention is optimal duration of continuation of therapy postpartum (4 weeks or 12 weeks) as the drug is excreted in breast milk and safety data on neonates is insufficient. In this study, the women were instructed not to breastfeed for 4 weeks in the treatment group. Besides viral load and HBeAg status, other factors responsible for true immunization failure like maternal cytokine polymorphism and transplacental infection are not eliminated with drug therapy.

Till date, treatment for hepatitis B infection in pregnant women is given routinely for mothers with advanced disease, acute exacerbation or in liver failure where maternal benefits outweigh fetal risks; its routine use to prevent perinatal transmission is not widely accepted. The present study indeed adds to the much needed good quality evidence, but larger trials with a longer follow-up in terms of efficacy, duration of treatment and maternal and fetal safety are required for routine practice. There is also a research gap to determine the optimal threshold of HBV DNA for antiviral therapy.

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Neonatologist's Viewpoint

Interruption of mother-to-child transmission of hepatitis B virus (HBV) infection is important not only for preventing chronic liver disease and hepatocellular carcinoma in the offspring but also from the perspective of reducing the global burden of chronic liver disease. Vertical transmission of hepatitis B accounts for almost half of the chronic liver disease seen worldwide, and India has the second largest pool of chronic HBV infection despite much lower seroprevalence than China and other Southeast Asian countries (0.9% *versus* 10-20%) [1].

Combined active and passive immunization is effective in reducing the perinatal transmission of HBV. Probability of infant being infected decreases from 90% to less than 10% with combined immunization [2]. However, probability of infant getting infected with HBV despite combined immunization is higher if mother is HBeAg-positive, has high HBV DNA load, is less than 25 years old or infant has not received the required 3 doses of hepatitis vaccine [2]. Overt HBV infection and poor response to hepatitis B vaccine is still common in neonates who receive both hepatitis B immunoglobulin and hepatitis B vaccine [3]. In this scenario, studies have indicated usefulness of nucleotide analogues in enhancing efficacy of combined immunoprophylaxis [4]. Recent update of Asian-Pacific clinical practice

guidelines recommend use of tenofovir or telbuvidine for reduction of risk of mother-to-infant transmission for women with HBV DNA more than 6–7 $\log_{10}$ IU/ml [5]. The randomized controlled trial by Pan, *et al.* [6] has strengthened the case for use of tenofovir to prevent hepatitis B transmission in pregnant women with high viral load (HBV DNA >200,000 IU/mL). In the intention-to-treat analysis, incidence of HBV infection in infants was reduced from 18% to 5.2% (number needed to treat: 8). Tenofovir did not have any significant adverse effect on mother, fetus or infant. Tenovofir was continued till 4 weeks postpartum and neonates were not breast-fed. However, accumulating evidence from HIV-positive mothers taking tenovofir suggestes that exposure to tenofovir is insignificant in a breastfed neonate and there are no significant adverse effects. However, based on current recommendations, mother should be counseled about suspending breastfeeding while she is taking tenofovir.

With current body of evidence, oral tenofovir prophylaxis must be offered to eligible HBsAg-positive pregnant women. This needs strengthening and standardization of laboratory monitoring and management planning. HBV-DNA levels and HBeAg status must be determined at beginning of third trimester in HBsAg-positive pregnant women, and those classified to have high replicative status should be managed at a tertiary care center by a team of hepatologist, obstetrician and neonatologist.

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