Antiviral treatment of HBV positive pregnant women: an additional tool to reduce perinatal transmission

Roberto Bruni[1], Gloria Taliani[2], Anna Rita Ciccaglione[1]

[1]Department of Infectious, Parasitic and Immunomediated Diseases, Istituto Superiore di Sanità, Rome, Italy, [2]Department of Clinical Medicine, Sapienza Università di Roma, Rome, Italy

In a recent study published in *New England Journal of Medicine*, Pan and colleagues[1] faced an important aspect for prevention of hepatitis B virus (HBV) infection: antiviral treatment with Tenofovir (TDF) during pregnancy to reduce perinatal transmission. This route of infection plays a crucial role for global diffusion of HBV, with frequency of chronic infection in mother-to-child-transmission (MTCT) of 90%.

The results by Pan and colleagues show that TDF treatment during pregnancy significantly reduces the transmission rate compared to the standard prophylaxis recommended by World Health Organization (WHO),[2] that leaves a residual HBV transmission mostly in highly viremic mothers (>200,000 IU/mL HBV-DNA). Thus, reduction of the viral load at delivery by antiviral treatment is an attractive possibility in reducing MTCT. Indeed, in a recent simulation model of the global HBV epidemic, scaling up the use of peripartum antivirals (to 80% of HBeAg positive mothers), together with other interventions, was indicated as an important strategy to avert 7.3 million deaths between 2015 and 2030.[3]

Earlier reports have shown conflicting results but, according to recent WHO guidelines,[2] quality scores of some studies were low, highlighting the need for further, more carefully designed ones. Pan et al. performed a multicenter, open-label, randomized, parallel-group study, enrolling 200 highly viremic mothers. The reliability of the results was significantly improved by a proper experimental design. The primary outcomes (transmission rate and birth defects) were assessed at 28 weeks after birth, a longer follow-up than in previous studies. In addition, monitoring of maternal viral load convincingly demonstrated, in 68% mothers, reduction of viremia at delivery below the 200,000 IU/mL, considered to be the threshold value for significant decrease of MTCT.

Coorespondence: Anna Rita Ciccaglione. Department of Infectious, Parasitic and Immunomediated Diseases, Istituto Superiore di Sanità, Rome, Italy. Email: annarita.ciccaglione@iss.it

The results support the efficacy of TDF to prevent MTCT in highly viremic mothers (median value: 8.18 log10 IU/mL or 151,000,000 IU/mL). Treatment was beneficial, since in the per-protocol analysis none of the infants born to compliant mothers resulted in infection by HBV compared to 7% of controls ($p = 0.01$). Moreover, the short-term safety reported in the study confirms data from HIV-infected pregnant women.[4] However, some fundamental questions remain unanswered.

The first regards the best time to start treatment during pregnancy. Treatment initiation may be a relevant issue since adherence may be suboptimal out of a controlled study, and there is a possibility that the later the treatment is started the more significant the effect of nonadherence is on the virological control. The antiretroviral pregnancy registry, which reports the overall rate of birth defects observed in children born to mothers treated during the entire pregnancy, indicates that such rates for lamivudine and TDF is similar to the general population (2.8% vs. 2.72%).[5] Therefore early treatment could be a viable option.

The second point is related to safety of breastfeeding in treated mothers. In the study of Pan et al., breastfeeding was banned for mothers taking TDF during the first four weeks after delivery. In HIV-mothers, TDF concentrations in breast milk are reported to be very low, ranging from 17.6 ng/mL to undetectable levels one week after delivery[6] and the median plasma concentration detected in breastfed children at 6 months of age was 24 ng/mL.[7] Examination of breast milk TDF concentration could have been an interesting result that arose from this study, but it was missed. However, preventing mothers to be breastfed may represent a significant problem in some highly endemic areas of the world where interrupting HBV MTCT is extremely important, but breastfeeding is an essential key resource.

Finally, the results of this study should prompt action to overcome the existing limitations. One of which could be the assessment of viral load in areas where HBV is highly prevalent but the economic resources are scarce.

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This will be seen in the form of a phase III, multicenter, placebo-controlled, double-blind, randomized (1:1) clinical trial that will be conducted in Thailand and will enroll more than 300 pregnant women, the only virological inclusion criterion will be HBeAg-positivity, irrespective of HBV-DNA level.[8] Examining the results of this trial will be extremely important to plan prevention campaigns, especially in countries with limited access to facilities with high virological diagnostic skills.

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