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Does currently recommended maternal antiviral prophylaxis against mother-to-child transmission of hepatitis B virus require enhancement?

To the Editor:

We read with interest the article entitled "Enhancing interventions for prevention-of-mother-to-child- transmission (PMTCT) of hepatitis B virus (HBV)" by Matthews *et al.*,[1] who comprehensively reviewed the measures for preventing MTCT of HBV. We consider that the proposals on the maternal administration of anti-HBV agents (nucleos(t)ide analogues [NAs]) to prevent MTCT of HBV should be viewed with caution.

Matthews *et al.* propose that maternal HBV DNA thresholds for antiviral prophylaxis may reduce from the current >2 × 10^5 (>200,000) IU/ml to ∼10^4 or even to 2 × 10^3 (>2,000), assuming that undetectable HBV DNA levels would mitigate any quantifiable transmission risk, based on the 'undetectable = untransmissable' (UU) paradigm for HIV.[1] However, HBV infection is different from HIV infection. All HIV-infected women, regardless of pregnancy, require antiretroviral therapy (ART), but most HBV-infected women at childbearing age are in an immunotolerant phase and do not require antiviral therapy. Moreover, since there is no effective vaccine or immunoglobulin against HIV, maternal ART is the most important measure to prevent MTCT. By contrast, MTCT of HBV can be efficiently prevented by combined immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine in neonates. Numerous studies have demonstrated that immunoprophylaxis protects almost all infants of mothers with HBV DNA ≤2 × 10^6 IU/ml from chronic HBV infection, and the lowest maternal HBV DNA level that causes failure of immunoprophylaxis is >2 × 10^6 IU/ml (Table S1 and S2). Thus, the currently recommended maternal HBV DNA threshold (>2 × 10^5 IU/ml) for antiviral prophylaxis against MTCT of HBV is conservative.

Currently, maternal antiviral prophylaxis against MTCT of HBV usually starts from the third trimester (gestation 28–32 weeks). Matthews *et al.* propose that maternal antiviral administration may start earlier in pregnancy, potentially as soon as maternal HBsAg-positive status is confirmed.[1] However, studies demonstrated that maternal administration of anti-HBV agents (including tenofovir disoproxil fumarate [TDF], and other anti-HBV agents) earlier than the third trimester did not further reduce MTCT of HBV.[2,3] In practice, after administration of antivirals in mothers with high viral loads and immunoprophylaxis in neonates, MTCT of HBV is almost completely blocked,[2–6] with MTCT rates as low as 0–<1% rather than 0–6%, which was mentioned in their article.[1] Thus, earlier administration of antiviral agents during pregnancy is less likely to further reduce MTCT of HBV.

It is generally considered that intrauterine NA exposure has no influence on the development of fetuses. However, severe congenital malformation (biliary atresia, congenital megacolon, and anotia), cerebral palsy, severe muscularly developmental abnormalities, fetal death, stillbirth, infant sudden death were repeatedly reported in fetuses/infants born to mothers who were treated with anti-HBV agents during pregnancy.[4–7] In addition, the frequency of premature birth in antiviral-treated pregnant women was higher than that in untreated pregnant women (13.1% [8/61] *vs.* 2.9% [1/34]).[8] More recently, studies have shown that, of 182 pregnant women who had received TDF before conception or within gestation week 12, 10 (5.5%) experienced miscarriages, 3 (1.6%) stillbirth, and 2 (1.1%) inductions of labor due to severe malformations, and of 417 pregnant women who had received telbivudine before conception or in the first trimester, 10 (2.4%) experienced miscarriages, 6 (1.4%) stillbirth, and 3 (0.7%) inductions of labor due to severe malformations.[9] Thus, the relationship between maternal NA administration and these severe adverse events cannot be completely excluded. The shortest period of fetal NA exposure is desirable as long as MTCT of HBV is prevented.

The safety data on maternal ART in HIV-infected pregnant women cannot be directly translated to maternal anti-HBV therapy. Maternal HIV infection can cause adverse pregnancy outcomes and congenital fetal abnormalities. In theory, maternal ART may decrease congenital fetal abnormalities after HIV viral loads were significantly inhibited. But maternal ART during pregnancy does not decrease congenital fetal abnormalities in infants, suggesting the potential adverse effects of maternal ART on fetuses. Actually, maternal ART may have other adverse effects on pregnancy.[10]

The cornerstone of preventing MTCT of HBV is to use both HBIG and hepatitis B vaccine in neonates. There is almost no concern on the safety of HBIG and hepatitis B vaccine. After timely immunoprophylaxis, MTCT rates in children of HBV-infected mothers with negative and positive HBeAg have been reduced from 10–30% to nearly 0% and from 70–90% to 5–10%, respectively. Administration of anti-HBV agents in mothers with high viral loads or positive HBeAg is a supplementary measure. The currently recommended neonatal combined immunoprophylaxis and antiviral prophylaxis in pregnant women with HBV DNA >2 × 10^5 or positive HBeAg, started from gestation 28–32 weeks, can almost completely prevent MTCT of HBV. Lowering the current viral load threshold and starting maternal prophylaxis before the third trimester are less likely to further reduce MTCT of HBV but may be associated with additional adverse pregnancy and neonatal outcomes.

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions
Yi-Hua Zhou and Hong Zhao both contributed to the conception, drafting and revision of this work.

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