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Choosing the appropriate pharmacotherapy for hepatitis B during pregnancy: what are the considerations?

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KEYWORDS Hepatitis B; HBV; mother-to-child transmission; vertical transmission; prophylaxis; prevention; tenofovir; antiviral

1. Introduction

In 2015, 3.5% of the world population, around 257 million people, was estimated to live with chronic hepatitis B virus (HBV) infection, mostly in the African and Western Pacific regions (68% of HBsAg carriers) [1]. HBsAg-positive population includes approximately 65 million women of childbearing age [1].

The fraction who become pregnant faces important challenges: the maternal and fetal hazards posed by the virus, as well as the risk of mother-to-child (MTCT) transmission [2].

Actually, data are mixed about the potential negative consequence of HBV on pregnancy outcomes: an increased risk (16%) of preterm birth has been described, but pooling low-quality and not-well controlled studies [3]. More robust data pointed out an adjusted higher odd (47%) of gestational diabetes mellitus in HBsAg-positive pregnant women [4]; nonetheless, in general no rock-solid evidence of relevant effects of the virus on other pregnancy outcomes has emerged [2].

The scenario is different if cirrhosis is present: cirrhosis was found to be an important predictor of adverse perinatal outcomes affecting both the mothers and products of conception in a large matched cohort enrolling more than 2000 pregnant women [5]. At any rate, cirrhosis is an uncommon occurrence in pregnant subjects: it results from a wide array of liver injury mechanisms and its final features are independent from the triggering process [5].

In turn, pregnancy may impact on the course of both acute and chronic hepatitis B owing to immunological modifications occurring in the women. About acute hepatitis B, actually clinical recovery and mortality rates are similar among pregnant and non-pregnant subjects, but pregnancy may favor chronicity by impairing HBsAg loss and seroconversion [6]. In women with preexisting chronic hepatitis B, on the one hand, viremia and viral antigens levels are quite stable during pregnancy; on the other hand, alanine aminotransferase (ALT) levels, mirror of infected liver cells destruction, may be lower before a potential increase (usually asymptomatic and self-limited) in the postpartum period due to immunological restitution [2].

Regarding vertical transmission (or MTCT), in areas characterized by high and intermediate endemicity (≥8% and 2–7% of HBV prevalence, respectively), it is the major driver of contagion [7]. Moreover, earlier is the age of acquisition, higher is the likelihood to develop chronic infection, up to 90% for infants infected perinatally [2].

The prevention of MTCT by employing all the available measures is the key component of the strategy to curtail the burden of HBV infection worldwide besides the implementation of universal vaccination for all the newborns [2,8].

2. Pharmacotherapy for HBV infection during pregnancy: rationale and criteria

The antiviral armamentarium against HBV is made of two classes of drugs: interferons (specifically alpha-type), available in injectable formulations, and oral nucleos(t)ide agents (NAs) [9–11]. The former, despite being the drugs of choice in case of co-infection with hepatis delta virus and offering the advantage of a finite treatment course, show an unfavorable side effect profile combined with a highly variable response; the latter thus are the first-line anti-HBV agents owing to their good safety profile along with a well-established effectiveness [9–11]. Among NAs, the newer-generation entecavir (ETV) and the two tenofovir prodrugs [tenofovir disoproxil fumarate (TDF) as well as tenofovir alafenamide (TAF)] are considered first-line agents and currently preferred over the older agents lamivudine (LAM), adefovir (ADV), and telbivudine (TBV) thanks to their higher genetic barrier to resistance [12].

The use of antivirals is mainly directed for chronic HBV infection, whereas their place in therapy for acute HBV is far more limited in the light of the high rate of spontaneous full recovery among adults, thereby NAs are advised only in case of severe or fulminant course, when even liver transplantation should be taken into account [13].

Beyond some slight differences among the main international guidelines [9–11], indications for treatment of chronic HBV infection are cirrhosis, ALT level greater than twice the upper limit of normal plus viremia > 20,000 International Units (IU)/ml, at least moderate liver fibrosis plus viremia >2000 IU/ml, and abnormal ALT level [14].

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When it comes to the potential use of anti-HBV agents in pregnancy, a fundamental point is the absolute contraindication to the use of interferons, thus the therapeutic armamentarium includes only NAs [15]. Oral anti-HBV drugs are not equal as for safety profile in pregnancy: among the first-line choices, tenofovir has been classified as a 'category B' agent (no risk for fetuses in animal reproduction studies) differently from ETV, classified as 'category C' due to its carcinogenic potential in animal studies [16]. With regard to tenofovir prodrugs, of course there is evidence accrued over several years supporting the use of TDF in pregnant women with HBV as stated by the guidelines [9–11]; preliminary data on TAF, only recently introduced in clinical practice, are reassuring [17], and results from ongoing clinical trials (NCT04237376, NCT04211805) are eagerly awaited to yield high-quality recommendations.

To simplify, the following scenarios may happen in pregnancy: a woman already on treatment or a pregnant individual not undergoing any therapy either because oblivious to her HBsAg-positive status (HBV screening is mandatory in the first trimester) or since not fulfilling the above-mentioned criteria for antivirals initiation [15].

In the first case, a careful reassessment of the appropriateness of therapy should be performed: not only contraindicated drugs (ETV, interferons) must be stopped, but the treatment itself may be discontinued if not strictly necessary (for instance, in the presence of mild hepatitis) [18]. Instead, when treatment continuation is unavoidable (e.g. cirrhotic woman), switch to TDF is advised if the subject is under another NA [16].

In the second case, a periodic evaluation is necessary to stage the liver disease and to establish whether antiviral treatment with TDF is necessary during pregnancy according to the above-mentioned criteria for chronic HBV infection, always in a risk–benefit perspective, or is deferrable after delivery [16]. As a matter of fact, there is no crystal-clear evidence that clinical or serological outcomes are improved by antivirals during pregnancy [2].

The last, but absolutely not the least, scenario to consider is the prevention of HBV vertical transmission. In the very large majority of cases, it happens during the peripartum period (>90%), whereas it is much less common in utero and turns out to be very rare in the postpartum phase (< 1%) [2]. The mainstay of HBV MTCT prevention is the immunoprophylaxis of the newborn, both active and passive, to be administered at birth [19]. Nevertheless, standard prophylaxis may fail in up to 10% of cases, so requiring additional preventative measures [2]. Avoiding breastfeeding and delivery through cesarean section is not recommended on the basis of current evidence [9–11]. Considering that, in addition to inappropriate immunization as for timing and/or schedule, the strongest predictor of immunoprophylaxis failure is represented by maternal viral load, antiviral treatment emerges as the most powerful additional preventive action [20]. To this regard, the seminal study by Zou and colleagues set the pre-delivery viremia threshold of 200,000 IU/ml (5.3 $\log_{10}$ IU/ml or 1,000,000 copies/ml): under this level, the risk of immunoprophylaxis failure was 0% [21]. HBeAg positivity is strictly associated with high serum HBV DNA values and may be used as an alternative to viremia determination in low-resource countries [2]; another potential alternative is HBsAg quantification, with proposed threshold equal to 4 $\log_{10}$ IU/ml [10].

Once decided for antiviral start to prevent HBV MTCT in women not previously on therapy, the final issues are timing and the agent of choice. Recommendations from authoritative international societies are in favor of TDF to be started at the beginning of the third trimester of gestation (28 weeks, not later than 32) until birth or up to 4–12 weeks after delivery [9–11]. Actually discontinuation of antivirals at the end of pregnancy, unless novel conditions arise (e.g. dramatic worsening of liver fibrosis), may be safely implemented since prolongation of therapy does not seem to affect outcomes such as postpartum ALT flares [2]. These indications were reinforced by a recent guideline from the World Health Organization [21], informed by a comprehensive systematic review and meta-analysis [22].

The latter focused on TDF, LAM, and TBV: all three drugs demonstrated efficacy and safety in reducing vertical HBV transmission without augmented risk of any maternal or infant safety outcome [22]. Pooled odds ratios (OR) of antiviral prophylaxis efficacy were similar among the agents under investigation (around 90% reduction of the odds of vertical transmission), but two factors confirmed TDF as the drug of choice: higher quality of evidence and superior barrier to resistance [21,22]. Interestingly, a post-hoc analysis showed the antiviral commencement in the second trimester (as early as 13 weeks) was better than the typical start in the last period of pregnancy: OR 0.23 (confidence interval 0.09–-0.59), but only four out of nine studies registered events (23 the total number) in one of the two arms, and TDF was the investigational drug in just two studies; therefore, these findings might be only hypothesis-generating at the most [22].

3. Expert opinion

As is well known, notwithstanding the long-established availability of effective vaccines and therapeutic agents, HBV infection is a relevant cause of morbidity and mortality: nearly 900,000 annual deaths were attributed to the virus in 2015 worldwide [1]. The vast majority of this health burden is related to chronic infection and to its main consequence, the development of cirrhosis: considering that evolution from acute to chronic state usually takes place when infection is acquired perinatally, prevention of HBV MTCT is a matter of utmost importance.

The use of anti-HBV agents in pregnant women may rely on maternal and newborn indications: in other terms, it is justified if the pregnant subject fulfills the standard criteria for anti-hepatitis B therapy in adults or if there is a substantial risk of immunoprophylaxis failure in the infant. Of course, the utilization of drugs in pregnancy should always derive from a careful assessment on a case-by-case basis.

Regarding maternal indications, postponing the treatment (of its continuation when started prior to pregnancy) should

Table 1. Recommendations from international guidelines regarding the use of antiviral agents in pregnant women as prophylaxis of HBV vertical transmission.

	Viremia threshold warranting treatment	Gestational age to start antiviral treatment (weeks)	Agent(s) of choice	Duration of treatment
APASL 2015 [9]	≥6–7 $\log_{10}$ IU/ml	28–32	TDF or TBV	Stop after delivery for breastfeeding
EASL 2017 [10]	≥5.3 $\log_{10}$ IU/ml	24–28	TDF	Up to 12 weeks after delivery
AASLD 2018 [11]	≥5.3 $\log_{10}$ IU/ml	28–32	TDF	Up to 4 weeks after delivery
WHO [21]	≥5.3 $\log_{10}$ IU/ml	28	TDF	Until at least childbirth

AASLD = American Association for the Study of Liver Diseases; APASL = Asian Pacific Association for the Study of the Liver; EASL = European Association for the Study of Liver; IU = International Unit; TDF = tenofovir disoproxil fumarate; TBV = telbivudine; WHO = World Health Organization.

be considered whenever possible since the benefits of antiviral therapy seem modest in terms of improvement of clinical and serological outcomes during gestation. In case of severe liver disease, start or continuation of treatment is warranted to avoid further worsening or decompensating events.

About vertical transmission prophylaxis, in Table 1 the current recommendations on antiviral use from most recent guidelines are summarized: they agree on the preferred agent (TDF) and on the viremia threshold warranting treatment, namely 200,000 IU/ml [9–11,21].

Nevertheless, some research gaps remain.

First, the exact timing of antiviral start. The beginning of the third trimester has been chosen to strike a balance between the necessity to have an optimal viral suppression by the end of gestation and the need to avoid unnecessary exposure to a drug in the first months of pregnancy. There is consensus on the week 28 as adequate starting point, but there is room for earlier initiation. European guidelines indicate 24–28 weeks as a potential range for antiviral beginning [10]. The recent meta-analysis by Funk and colleagues suggests that even more precocious start (at the beginning of the second trimester) may be feasible and effective [22]: pending further, more solid data, an earlier approach could be taken into account in particular situations, such as very high maternal viral load (≥8 $\log_{10}$ IU/ml) [2] or planned invasive prenatal tests (e.g. amniocentesis, that increases MTCT risk) [23].

Second, the alternatives to TDF. The most obvious would be TAF, but more evidence in pregnant women is needed. Instead, the experience of TDF in pregnancy is large and is mostly derived by studies on human immunodeficiency virus: indeed, it is still today one the reference drugs as backbone in pregnant women under antiretroviral treatment [24]. In this perspective, the potential use in pregnancy of upcoming novel agents (entry inhibitors, antisense oligonucleotide core protein allosteric modulators, checkpoint inhibitors, therapeutic vaccines) would need specific assessment [25]

Third, it is to be established the precise duration of antiviral treatment, whether it should be stopped at childbirth or prolonged for some weeks. The extension of therapy after delivery is a matter weaving together many aspects: the potential interference with breastfeeding, the suppression of ALT flares, the reassessment of liver disease, the theoretical risk of resistance selection, especially when subsequent pregnancies are possible and intermittent antiviral administration (only during gestation) might not be a good strategy to control viral replication.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Global hepatitis report. WHO; 2017 [cited 2020 Dec 23]. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/
2. Terrault NA, Levy MT, Cheung KW, et al. Viral hepatitis and pregnancy. Nat Rev Gastroenterol Hepatol. 2020;18:117–130. Published online 12 October 2020

•• **Very comprehensive review addressing the issue of viral hepatitis in pregnancy, including HBV.**

3. Ma X, Sun D, Li C, et al. Chronic hepatitis B virus infection and preterm labor(birth) in pregnant women-an updated systematic review and meta-analysis. J Med Virol. 2018;90:93–100.
4. Tan J, Mao X, Zhang G, et al. Hepatitis B surface antigen positivity during pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. J Viral Hepat. 2018;25:1372–1383.
5. Flemming JA, Mullin M, Lu J, et al. Outcomes of pregnant women with cirrhosis and their infants in a population-based study. Gastroenterology. 2020;159:1752–1762.
6. Han Y-T, Sun C, Liu C-X, et al. Clinical features and outcome of acute hepatitis B in pregnancy. BMC Infect Dis. 2014;14:368.
7. MacLachlan JH, Cowie BC. Hepatitis B virus epidemiology. Cold Spring Harb Perspect Med. 2015;5:a021410.
8. Orlando R, Foggia M, Maraolo AE, et al. Prevention of hepatitis B virus infection: from the past to the future. Eur J Clin Microbiol Infect Dis. 2015;34:1059–1070.
9. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1–98.

10. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–398.
11. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560–1599.
12. Seto WK, Lo YR, Pawlotsky JM, et al. Chronic hepatitis B virus infection. Lancet. 2018;392:2313–2324.
13. Yuen MF, Chen DS, Dusheiko GM, et al. Hepatitis B virus infection. Nat Rev Dis Primers. 2018;4:18035.
14. Tang LSY, Covert E, Wilson E, et al. Chronic Hepatitis B infection: a review. JAMA. 2018;319:1802–1813.
15. Maraolo AE, Gentile I, Buonomo AR, et al. Current evidence on the management of hepatitis B in pregnancy. World J Hepatol. 2018;10:585–594.
16. Aslam A, Campoverde Reyes KJ, Malladi VR, et al. Management of chronic hepatitis B during pregnancy. Gastroenterol Rep (Oxf). 2018;6:257–262.
17. Ding Y, Cao L, Zhu L, et al. Efficacy and safety of tenofovir alafenamide fumarate for preventing mother-to-child transmission of hepatitis B virus: a national cohort study. Aliment Pharmacol Ther. 2020;52:1377–1386.
18. Visvanathan K, Dusheiko G, Giles M, et al. Managing HBV in pregnancy. Prevention, prophylaxis, treatment and follow-up: position paper produced by Australian, UK and New Zealand key opinion leaders. Gut. 2016;65:340–350.
19. Borgia G, Maraolo AE, Gentile I. Hepatitis B mother-to-child transmission and infants immunization: we have not come to the end of the story yet. Infect Dis (Lond). 2017;49:584–587.
20. Cheung KW, Seto MTY, Lao TT. Prevention of perinatal hepatitis B virus transmission. Arch Gynecol Obstet. 2019;300:251–259.
21.) Prevention of mother-to-child transmission of Hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy. WHO; 2020 [cited 2020 Dec 23]. Available from: https://www.who.int/publications-detail-redirect/978-92-4-000270-8
• **The most recent authoritative guidelines focusing on antiviral use in pregnancy to prevent MTCT of HBV.**
22. Funk AL, Lu Y, Yoshida K, et al. Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis. Lancet Infect Dis. 2021;21:70–84.
23. Han Z, Yuan Z, Bai X, et al. Mother-to-child transmission of hepatitis B virus after amniocentesis: a retrospective matched cohort study. Prenat Diagn. 2019;39:431–440.
24.) Guidelines for the management of people living with HIV (PLWH) in Europe. EACS; 2020 [cited 2020 Dec 23]. Available from: https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html
25. Naggie S, Lok AS. New Therapeutics for Hepatitis B: the Road to Cure. Annu Rev Med. 2021;72:93–105.