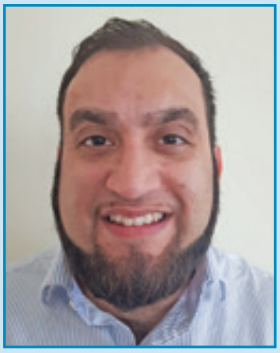
Chronic viral hepatitis B in pregnancy: clinical case presentation and guidelines review



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Summary

Hepatitis B virus infection during pregnancy presents with unique management issues for both mother and fetus. These include the effects of hepatitis B virus on maternal and fetal health, the effects of pregnancy on the course of hepatitis B virus infection, treatment of hepatitis B virus infection during pregnancy, and prevention of mother-to-child transmission. Clinical case and review of EASL guidelines are presented in this article.

Keywords: Hepatitis B virus, chronic hepatitis B, pregnancy, mother-to-child transmission, hepatitis B immunoglobulin, tenofovir.

Introduction

The World Health Organization (WHO) have identified mother-to-child transmission (MTCT) as being a key intervention in reducing the global prevalence of hepatitis B virus (HBV) infection. MTCT is not the only concern (1) in regard to HBV in pregnancy. Altered immune activity can affect the natural course of HBV and thus produce a flair in the virus; which is why many specialists systematically check viral loads in pregnancy.

Clinical case

In the interest of patient confidentiality, the clinical case discussed will be referred to as patient A. Patient A is a 39-year-old female from Vilnius, Lithuania whom was diagnosed with having chronic hepatitis B since 2002. Currently she is a mother of two children. Patient A has been particularly difficult to treat since her diagnosis and has presented many challenges to the infectious disease specialists looking after her in Vilnius, Lithuania. Aged 18 she was diagnosed with Hodgkin's Lymphoma which was successfully treated by the onco-haematologists. Chronic autoimmune thyroiditis, hypothyroidism have also been diagnosed for her. It was suspected, that hepatitis B virus infection was acquired by the patient during her treatment for Hodgkin's Lymphoma in the onco-haematology department. She had no blood transfusions or history of IV drug abuse (IVDU) or tattoos, while the parents and husband have no signs of infection as well.

HBeAg (+) chronic hepatitis B (CHB) was diagnosed in 2002: ↑ALT – 53 U/L –> 83 U/L, HBsAg (+), HBeAg (+), anti-HBc (+), anti-HBe (–), HBV-DNA (+), with a high viremia $>10^6$ copies/ml. Liver biopsy confirmed the CHB diagnosis (B18.1). Concomitant diseases were chronic autoimmune thyroiditis, hypothyroidism. Lymphogranulomatosis, in remission from 2003. In November 2003 antiviral CHB treatment with standard interferon alfa-2b (Realdiron) 6 MU TIW was started. Patient suffered from interferon treatment, she had influenza like side effects and signs of exacerbation of her chronic thyroiditis. The liver enzymes (ALT) activity increased but later subsequently decreased from 339 U/L to 46 U/L. No seroconversion of HBeAg was identified and high viremia levels still remained at $>10^7$ copies/ml. At treatment week 24 (May 2004), it was decided to extend the treatment for a further 24 weeks and also add a nucleotide analogue (NA) Lamivudine 100 mg OD in combination with interferon. After one month, due to exacerbation of autoimmune thyroiditis, the treatment with Realdiron

was discontinued. The treatment with Lamivudine was continued for 40 months (up to Nov 2006). During two years of treatment with Lamivudine (May 2004 – Jun 2006) liver enzymes activity was within the normal range (ALT – 38 U/L (2004) –> 35 U/L (2005) –> 45 U/L (2006)), viral levels slightly decreased (HBV-DNA – 3.49 x 10^5 IU/ml (2005) –> 3.17 x 10^4 IU/ml (2005)), but unfortunately there was no signs of HBeAg (+) or HBsAg (+) seroconversion. Signs of biochemical relapse and resistance to Lamivudine became evident from Jun 2006, when an increase in liver enzymes appeared: ALT – 45 U/L (Jun 2006) –> 70 U/L (August 2006) –> 93 U/L (November 2006) and still no HBeAg seroconversion and a high viral level persisting: HBV DNA – 6.8 x 10^7 IU/ml. In November 2006 it was decided to combine therapy with the use of Realdiron in conjunction with Lamivudine for a further 24 weeks and to reassess in May 2007. Slight biochemical activity remained at the end of treatment but still no seroconversion was forthcoming (↑ALT – 74 U/L, ↑AST - 47 U/L) and HBsAg (+), HBeAg (+), HBV-DNA – 3.2 x 10^8 IU/ml). Signs of chronic hepatitis B with expressed HBV replication remained: HBsAg (+), HBeAg (+), anti-HBe (–), HBV- DNA (+) –3.25 x 10^9 IU/ml (1.11 x 10^9 copies/ml).

Patient become pregnant and in 2008 successfully delivered a baby boy. In line with procedure the newborn was within twelve hours post-delivery given the hepatitis B vaccine and due to high viremia, the specific hepatitis B immunoglobulin (HBIG). Sadly, within four months the child was diagnosed with acquired HBV infection with signs of chronicity, infected via the MTCT route. The prophylaxis failure was attributed to the fact that mothers viral load (>10^7 IU/ml) was very high. It had been established that patient A become resistant to Lamivudine in 2006 so therefore the recommended treatment in pregnancy was not administered to patient A, while the newer class of anti-viral drugs such as Entecavir and Tenofovir were not reimbursed at the time through the national Lithuania medical insurance policy. Post-delivery patient A showed signs of very active HBV infection: ALT – 68 U/L (2009) –> 65 U/L (2010) –> 40.8 U/L (2010), AST– 46 U/L –> 37.8 U/L –>31.5 U/L, HBV-DNA – 2.06 x 10^8 IU/ml (2010) –> 6.09 x 10^7 IU/ml (2010). In December 2010, patient A once again become pregnant and subsequently successfully delivered her second child. The same challenges presented itself in this pregnancy as the first; a substantial MTCT risk from HBV and a virus that is actively replicating. In a change of management, it was decided to treat patient A with Lamivudine 100 mg QD during her third trimester. In 2011 patient A gave birth to a boy and was immediately given the HBV vaccine and the HBIG twice; 12 hours post-delivery and at two weeks of age. The child successfully did not acquire the HBV infection. Treatment with Lamivudine continued for eight months until July 2011. HBV DNA while on Lamivudine was still high (HBV-DNA – 61 317 585 IU/ml (Feb 2011) > 117 020 235 IU/ml (May 2011). HBV was already resistant to Lamivudine. In July 2011 the National Health Insurance Fund agreed to cover the treatment costs of Entecavir so therefore Entecavir 1.0 mg QD was administered and treatment was continued for almost 3.5 years. During the treatment with Entecavir the viral load was less than optimal. After nearly 3 years of treatment it remained very high (HBV DNA – 3.2 x 10^5 IU/ml). According to the European Medicines Agency (EMA) own official summary [8] of the medication use in patients HBeAg (+) CHB, the treatment of the patient with Entecavir is to be adjusted by 1.0 mg QD and in case of chronic HBV infection resistant to Lamivudine, there is a higher risk of resistance to Entecavir also. This is independent of the severity of hepatic disease that already exists. The complications of an increase in the viral load of HBV are potentially severe, therefore according to the EMA it is purposeful to prescribe such patients with a combination of Entecavir and other antiviral that does not have cross resistance with Lamivudine or Entecavir, or just to switch treatment with Entecavir to Tenofovir. [8]. In February 2014 it was decided to adjust patient's treatment plan due to resistant encountered so far using Lamivudine and Entecavir. An application was therefore made to the National Health Insurance Fund in Lithuania to cover the cost of Tenofovir 245mg QD. In October 2014 treatment with Entecavir was stopped and switched to Tenofovir 245 mg QD. Her last treatment results thus far are outlined below: ALT – 29.03 U/L (2018) AST – 20.18 U/L (2017); PLT – 207 x 10^9/1 (2018); HBsAg (+), HBeAg (+), anti-HBe (–) (2018); HBV-DNA: 272 545 IU/ml (10.2014) – 7205 IU/ml (11.2014) – 360 IU/ml (01.2015) – 61 485 IU/ml (04.2015) – 770 IU/ml (09.2015) – 45 IU/ml (04.2016) – 9 IU/ml (06.2017) – 10 IU/ml (01.2018) – 5 IU/ml (08.2018). Treatment with Tenofovir is continued. Patient's condition is well, the HBV infection is in remission with the viral load close to undetectable.

Discussion

As demonstrated in the clinical case history, treatment has been difficult and challenging in many aspects; however the primary focus of this clinical case presentation is to assess the treatment phase of patient during her pregnancy and immediately after delivery; although it must be highlighted how important the holistic treatment plan of HBV infection is and how inevitably it has an impact on treatment during the pregnancy.

Patient's diagnosis in 1998 of Hodgkin's Lymphoma is an interesting observation in paper of Farcucci et al. The association of hepatitis B virus infection

with B-cell non-Hodgkin lymphoma – a review [2] has argued that 'Epidemiological studies performed over the last decade have demonstrated a positive association between persistent, hepatitis B surface antigen HBsAg (+) CHB and B-cell non-Hodgkin lymphoma (NHL), with HBV-infected patients having a 2-3-fold higher risk to develop NHL than non-infected patients. [2].

Active CHB was still present despite the several treatment modalities given in order to achieve seroconversion and reduce the viral load. It must be noted however that other treatment options, such as newer antivirals, due to lack in the health care funding have not been available at certain time in Lithuania.

In the updated EASL clinical guidelines of 2017 a series of important recommendations were put forward. Establishing HBsAg screening in the first trimester is now widely accepted to be a strong recommendation amongst ante natal clinics globally. The benefits are obvious in that early management structures can be put into place once a positive result is attested for. Clinicians are able to plan any treatment in the third trimester as well as crucially advise on the vaccination and HBIG therapy that may be required upon deliverance of baby. Not only is this important for the child, as children, unlike adults who contract the virus early on, become chronic carriers in the majority of cases; but also, epidemiologically speaking preventing MTCT is crucial in stemming the prevalence of HBV within society. Women of childbearing age without advance fibrosis and planning a future pregnancy soon may be able to delay therapy until the child is born according to EASL guidelines (Evidence level II-2, grade of recommendation 2) [3]. Some women with CHB require antiviral therapy to prevent progression of liver disease (e.g. those with immune-active hepatitis), while others can be observed. The decision to initiate therapy while pregnant depends upon the presence or absence of cirrhosis, HBeAg, and hepatitis B e antibody (anti-HBe), as well as the HBV DNA and aminotransferase levels. The indications for antiviral therapy in pregnant women are generally the same as those for patients who are not pregnant. Antiviral therapy is recommended for patients with a persistently elevated ALT >2 times the upper limit of normal and an elevated HBV DNA (HBV DNA >20,000 international units (IU)/ml in HBeAg (+) patients or HBV DNA ≥2 000 IU/ml in HBeAg (–). However, in pregnant women without cirrhosis, some scenarios may differ. A woman may choose to defer therapy until after delivery if she has evidence of mild disease activity, such as ALT levels just above the treatment threshold. By contrast, a woman with a viral load >2 x 10^5 IU/ml should initiate therapy in the third trimester even if the ALT levels are normal. In this setting, the goal of therapy is to prevent transmission to the child. Tenofovir (TDF) is preferred if antiviral therapy is contemplated in pregnant women because of its potency, safety profile, and low risk of resistance.

Patient A's case clearly highlights how important it is to treat mother in third trimester in order to bring down the viremia as low as possible. The current recommendation is to prescribe TDF and to follow through with the combo prophylaxis of baby. The viremia cut off used for deciding to treat mother varies worldwide, however according to EASL guidelines that stands at anything > 20,000 IU/ml. In pregnant women already on NA therapy, TDF should be continued while ETV or any other NA should be switched to TDF (Evidence level II-2, grade of recommendation 1) [3].

In all pregnant women with high HBV DNA levels [200,000 IU/ml] or HBsAg levels [4 log10 IU/ml], antiviral prophylaxis with TDF should start at week 24–28 of gestation and continue for up to 12 weeks after delivery (Evidence level 1, grade of recommendation 1) [3]. It is important to continue TDF post-partum as HBV flares can occur. In patient A's case, post-delivery of her first baby her viremia jumped up to 6.09 x 10^7 IU/ml hence if she would be treated with TDF it would not have only helped manage her viremia in third trimester and subsequent transmission risk to baby but also could have kept her post-partum flare in check. The added benefit is that TDF treatment is not a contraindication for breast feeding as only concentrations of small oral bioavailability have been demonstrated far [3]. Safety of NA therapy during lactation is an unknown. While HBsAg has been detected in breast milk it is not considered a contraindication to breast feed for HBsAg positive mothers (Evidence level III, grade of recommendation 2) [3]. Presumably the levels being so low as to not outweigh the benefits of breast feeding.

Prevention of perinatal transmission is an important aspect along with treatment of mum in the challenge of HBV in pregnancy. Transmission is said to occur at delivery which is why recommendations are strong to give a combination prophylaxis of HBV infection immediately [4]. HBIG and the hepatitis B vaccine is the mainstay prophylaxis with each given to the baby at two different injection sites. Although most guidelines and countries have now adapted the an active prophylaxis of HBV infection to prevent passive approach to MTCT there are still questions over the level of efficacy of the approach. In the UK, HBIG is given if the HBV DNA is > 1,000,000 IU/ml or the birth weight of the child is < 1 500g [5]. This is generally correlated with if the virus is actively replicating by being HBeAg positive or the mother has acquired acute hepatitis B. Vaccination program in the UK has been modified since August 2017 worrying data that showed an increase [6] in the prevalence of the virus. Now all children are routinely vaccinated at 8, 12 and 16 weeks while those with mothers whom are classified as high risk or HBsAg positive the

child is given additional doses at birth (ideally within 12 hours), 4 weeks and one year of age.

The rate of perinatal transmission drops from a massive 90% to 10% in combination therapy [7]. The combination prophylaxis failures are almost exclusively reported in mothers who are HBeAg positive with high HBV DNA levels >200,00 IU/ml and/or HBsAg >2-4.5 log 10 IU/ml [3]. This is highlighted in patient A where she had a viral load $>10^7$ IU/ml. Despite the receipt of passive and active vaccination, HBV transmission occurs in up to 25% of infants born to mothers with HBV DNA levels greater than 200,000 IU/ ml.

The treatment for CHB is complex. TDF is now the choice of treatment but as we saw in patient A's treatment it is not always available. The three antivirals that are considered safe in pregnancy are Lamivudine (LAM), Telbivudine (TBV) and Tenofovir disoproxil fumarate (TDF).

Neither LAM, TBV or TDF is associated with premature birth, lower Apgar scores, or congenital malformations [8]. The exact timing of treatment initiation during the third trimester is not defined although EASL guidelines favor treatment from somewhere in between 28–32 weeks. 28 weeks would be ideal in order to allow sufficient time for the viral load to decline to <200,000 IU/ml by delivery.

Whether obstetric factors are associated with MTCT is not clear. Risk for MTCT is largely due to infant exposure to vaginal blood and secretions at the time of delivery. The obvious alternative is a cesarean section to reduce the risk of transmission but data on benefits of a C-section are unclear [8]. The benefits of natural delivery are well established so therefore in absence of clear contraindications a woman's HBV status should not determine the delivery method chosen; was there to be a C-section the indications would be obstetric.

Drug resistance, especially antibiotic resistance, is a well-known current health concern. It is a significant scientific and medical topic and out of the scope of this current review, however it must be highlighted resistant strains of HBV to current drugs is increasing and caution is needed to prescribe the correct drug at the correct dosage for the correct amount of time. Once resistant is certain serious alternatives needs to be looked at for treatment. Preventing transmission is not only important to stop the spread of HBV but stopping the hard treatment strains from spreading.

Conclusions

Management of HBV infection is challenging, long term and complex as it is but coupled with pregnancy the challenge is only magnified. The notion of multidisciplinary care is brought to the forefront when managing pregnant woman with HBV infection, with many specialists and teams involved to ensure good care of mother, baby and to look after the epidemiological risk factors associated with HBV; which may include screening and subsequently immunization of sexual partners and household contacts.

In fact, in relation to the 2017 EASL guidelines it may now be prudent to assess and hold treatment during pregnancy for those with advanced fibrosis; albeit the argument being in such circumstances the benefits are not outweighing the risks taken for fetus. When HBV infection is picked up during the early pregnancy screening assessment, decisions need to be made quick; essentially does mum need treatment and if so what to give and when. This is all done in light of a patients specific subsequent full HBV serology taken into account, but the default position is according to EASL 2017 guidelines to prescribe Tenofovir in case of viral loads > 200,000 IU/ml at 28–32 weeks` gestation.

Given the benefits of breastfeeding and the small risks of oral bioavailability of the newer antiviral drugs along with very small concentrations of HBV found in breast milk it is advised for chronic HBV mothers to breastfeed.

The combination prophylaxis should be given once HBsAg positivity is established; per guidance of many esteemed healthcare organizations such as EASL, American College of Gastroenterology, World Health Organization and national guidelines of leading healthcare nations. HBIG must be given in cases of high viremia (>200,00 IU/ml). In any case of HBV risk or positive serology the newborn accelerated vaccination programme must always be followed.

Straipsnis recenzuotas

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