Preventing vertical hepatitis B transmission across all borders: A review of current concepts

Gemma M Daley
Fourth Year Medicine (Undergraduate)
James Cook University

Gemma, currently studying at JCU, has a passion for women's health and paediatric medicine. She is interested in practising in developing communities and research pertaining to this.

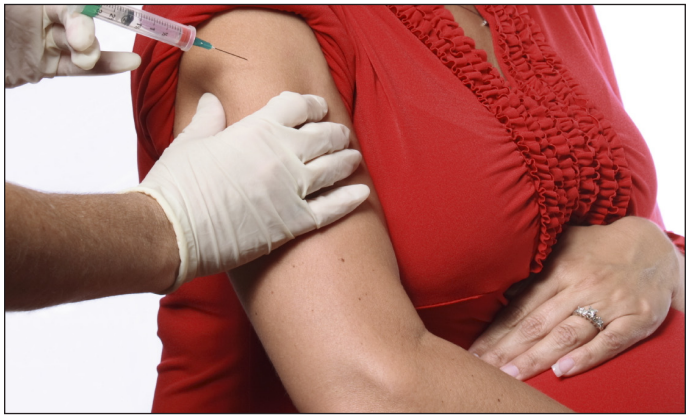
Aim: The aim of this review is to emphasise the global significance of Hepatitis B (HBV) and its vertical transmission, and to summarise the current status of preventative strategies. **Methods:** A literature review was carried out. PubMed, The Cochrane Collaboration and Medline were searched for both primary studies and reviews pertaining to vertical HBV transmission, its prevention and barriers to prevention. Key words used included "HBV," "Hepatitis B," "vertical transmission," "mother to child transmission," "prevention" and "epidemiology." **Results:** HBV is a major cause of death from liver cancer and liver failure. HBV is the ninth leading cause of death internationally and accounts for up to 80% of the world's primary liver cancers. In highly endemic areas, 75% of chronic HBV is acquired by vertical transmission (mother to child transmission at birth), or by horizontal transmission in early childhood. The earlier in life the disease is acquired, the greater the adverse consequences. Available therapies for preventing mother to child transmission are very effective and include multiple doses of HBV vaccine and usually, HBV immunoglobulin. However, up to 10% of infants acquire HBV despite this standard prophylaxis. Whether anti-viral agents should be given to mothers with a high viral load to prevent transmission remains controversial. **Conclusion:** HBV is an extremely important global public health issue. Prevention of vertical transmission is the most important preventative strategy and current prophylactic therapies are highly effective. Emerging approaches for mothers with a high viral load require further investigation to determine whether they are effective and safe. Developing countries face the issues of cost, access and education to apply prevention strategies, while developed countries need processes to ensure adherence to established recommendations.

Introduction

Infection with Hepatitis B virus (HBV) is a global health issue. Liver damage is the major complication of HBV infection. Such damage may be acute or chronic and results from an immune response to the virus. The acute hepatitis syndrome varies from a mild asymptomatic presentation to a severe, even fatal illness. Chronic infection with HBV is a more significant international public health issue than the acute illness. Chronic hepatitis is more common and has the potential to cause significant morbidity and mortality due to a resultant cirrhosis and/or hepatocellular carcinoma. [1-4] One third of the world's population is estimated to have once been infected with HBV, with an estimated 360 to 400 million chronic carriers internationally. Importantly, each year, approximately one million deaths are caused by HBV, making it the ninth leading cause of global mortality. [3,5-7] This is a critical health issue to address.

Mother to child transmission (MTCT) is of great importance for two main reasons. Firstly, it is a numerically important mode of transmission; and secondly, the earlier an individual is infected, the more likely it is that chronic infection will result. [8-11] If the individual is an infant at the time of infection, a 90% chance exists that they will develop a chronic infection. In contrast, if an individual is an adult at the time of infection, they have a 6% to 10% chance of the infection becoming chronic; a much lower probability. [3,12,13] Therefore, understanding this mode of transmission is very important in reducing the morbidity and mortality inflicted by HBV.

Although vertical transmission may be perceived as a major problem,



it also presents a major opportunity for effective intervention. For the purpose of this investigation, vertical transmission includes antenatal transmission via the placenta, transmission during delivery and postnatal transmission from mother to child during infancy. [14]

International epidemiology

Prevalence of HBV (defined as the proportion of individuals with HBV surface antigen positive status) varies significantly between countries. Certain areas of the world are classified as having high prevalence (>8%) including China, South-East Asia and sub-Saharan Africa; intermediate prevalence (2-7%), in southern and eastern Europe; and low prevalence (<2%) in Western Europe, North America and Australia. [15-18] However, even within low prevalence regions there are ethnic groups with high carrier rates that require special consideration. The highest rates of HBV carriers are found in developing countries, attributable to a multitude of factors including insufficiency of medical facilities and lack of education. [19]

Unfortunately, there is a lack of information regarding the global burden of HBV. In response to this deficit a mathematical model was constructed in 2005 which estimated the annual mortality rate for HBV-related disease to be 620,000. From these findings it was then proposed that 94% of these HBV-related deaths occurred as a result of chronic infection-related cirrhosis and hepatocellular carcinoma, while only 6% of these deaths could be attributed to acute hepatitis B. [20] In contrast, the World Health Organisation (WHO) has estimated a total annual mortality relating to HBV and the development of chronic clinical forms to be one million. [5]

Of the 360 to 400 million chronic HBV carriers worldwide, it is hypothesised that one quarter will die of liver disease as a result of their carrier state. [5,21] Despite the differences in the absolute values reported in the literature, it is clear that chronic HBV infection is a major health issue. Of particular relevance to this review, in the highly endemic aforementioned areas, up to 75% of chronic carriers acquire HBV by vertical transmission. [19,20,22] HBV also causes 60% to 80% of the world's primary liver cancers. [19,23] It is therefore evident that preventing vertical transmission is a critically important measure in disease prevention.

Mechanisms of vertical transmission

Vertical transmission of HBV incorporates a number of routes of infection. In particular, this term refers to transmission during pregnancy (antenatal), at the time of birth (at parturition) and after delivery (postpartum). However, it is important to note that most

transmissions from mother to child occur during parturition.

Antenatal transmission
Intrauterine infection is the mechanism by which the fetus is infected during the antenatal period. [15] It is estimated that this mode of transmission accounts for 10% to 44.4% of infection in at-risk infants. [15,24,25] This is thought to happen through the placenta, either by "cellular transfer" or by transplacental leakage of maternal blood. [14,15,26,27] The major risk factors for intrauterine transmission include premature labour, HBV DNA of cord blood and mothers of HBeAg-positive status. [24,28,29] Viral structure, HBV mutations, placental barrier and the immune status of the mother and of the fetus have also been implicated. [29] It has also been proposed that antenatal HBV transmission can occur through infected oocytes but this is yet to been confirmed. [15]

The issue of whether invasive procedures undertaken during pregnancy increase the risk of HBV transmission is debated. A relatively small amount of research considers if amniocentesis or chorionic villous sampling increases the risk of HBV transmission to the fetus in HBV infected mothers. The general consensus is that this risk seems to be low when the procedure is performed accurately. [21,30-34] This is an area of research that needs to be investigated further to reach a conclusion.

Transmission during parturition
This route of transmission arguably poses the greatest threat to the infant. HBV-DNA has been detected in amniotic fluid samples and vaginal secretions. [5,15] It is controversial as to whether delivery via caesarean section is beneficial in these individuals. [10]

Postnatal transmission
Postnatal transmission is believed to occur through body fluid interacting with mucosal surfaces. [3,35] Transmission occurs if the infant is in close contact with infected individuals. Whether breastfeeding increases the risk of transmission remains controversial. [10]

Current preventative strategies and their efficacy

Current preventative strategies include active (Hepatitis B vaccine) and/or passive prophylaxis (Hepatitis B immunoglobulin).

Hepatitis B virus vaccine
There are two licensed forms of the hepatitis B vaccine (HBVac), plasma-derived and recombinant. Both are effective, with no significant difference in hepatitis B occurrence between either product following administration. [16,36] These vaccines are composed of the HBV surface antigen, commonly referred to as HBsAg, exposing the most immunogenic epitope on the surface of the vaccine particles. [19] Completion of the vaccination program in healthy individuals induces protection in about 95% of cases. [19,37] Without HBVac, the mortality associated with both the acute and chronic infections is predicted to rise dramatically. [20]

HBVac has proven to be efficacious. The vaccination alone is 90% effective in preventing vertical transmission when administered to newborns. In addition, vaccination of newborns provides pre-exposure prophylaxis to infants born to women without hepatitis B, reducing the risk of becoming a chronic carrier in infancy and early childhood (prevention of early horizontal transmission). [38-40] This is particularly important in highly endemic areas.

Hepatitis B immunoglobulin
Hepatitis B immunoglobulin (HBIG) is a purified solution derived from human plasma containing large amounts of antibodies to HBsAg (anti-HBs or HBsAb). This substance is derived from donations given by immune individuals. [5,8,41] HBIG significantly reduces hepatitis B occurrence when compared with placebo or no intervention. HBIG is effective immediately following administration providing a high level of infant protection for a number of months. [16]

Combination of HBV vaccine and HBIG
Studies have proposed that the combination of neonatal HBVac and HBIG administration is more effective than either strategy alone. [16,42,43] This combination of HBIG at the time of birth and the completion of a HBVac program over the first six months of life is effective in preventing perinatal transmission and is routine in most countries. [44]

The contemporary challenge is that despite combined (active and passive) neonatal immunoprophylaxis, around 10% of neonates born to HBV carriers will become chronically infected. [16,42]

Current recommended prophylaxis protocol

Screening is critical in identifying which of the mothers are positive for HBV. It has been recommended that all pregnant women undergo prenatal screening for HBsAg to identify which neonates will require prophylaxis. [38,45]

Considering that HBV is such a burden on international public health, there is a need for a uniform prevention protocol. Currently, the WHO, World Gastroenterology Organisation (WGO) and the United States (US) Centers for Disease Control and Prevention (CDC) all recommend joint HBV immune prophylaxis. This includes HBVac and hepatitis B immunoglobulin within 24 hours after birth. [8,38]

These recommendations are supported by a number of trials in which HBVac and HBIG administered to the neonate were beneficial in the prevention of vertical transmission. [8,38,46]

Emerging and controversial prophylactic therapies

Due to the inability of routine prophylaxis administered postpartum to prevent all cases of MTCT, there is cause to investigate other possible interventions. Those currently being investigated and trialled include the administration of HBIG during the third trimester and antiviral therapy in the third trimester.

HBIG during the third trimester
Despite remaining a controversial topic, many studies have found a decrease in the percentage of chronic HBV infections in infants, even when used in combination with routine prophylaxis of HBVac and HBIG post-partum. [8,10] Interestingly, it is also being proposed that HBIG enhances the immune response to HBVac. [8,42]

In a recent (2010) cohort study, the rate of vertical chronic HBV transmission was only 4% when mothers received HBIG in combination routine prophylaxis. [8,10]

In addition to reducing the percentage of chronic HBV infections, HBIG has also been implicated in a subsequent increase in neonatal HBsAb seropositivity and a lower rate of intrauterine infection following administration; [8,21,47] however, this has not been a consistent result.[8,42,48]

While still unclear, the proposed mechanisms behind the interruption of HBV transmission are as follows. HBsAg is bound by HBsAb (from the HBIG) which stimulates the complement system. This enhances humoral immunity resulting in a reduced maternal HBV load, protection of uninfected cells and inhibition of viral replication. It is possible that HBIG facilitates a passive foetal immunity. [49,50] In contrast, another study has suggested that HBIG neutralises HBV in the maternal blood thereby reducing the risk of intrauterine infection. [8,42,51] This area of research is still under investigation. It will be particularly important to consider this prophylactic measure in mothers whose infants are in the high risk groups.

Antiviral therapy during the third trimester
Antiviral therapy during the third trimester is the emerging prophylactic approach of the greatest contemporary interest (Figure 1). The main antiviral agents being considered in this context include lamivudine, tenofovir and telbivudine. Lamivudine works by blocking HBV DNA polymerase. In doing so, it inhibits the synthesis of DNA and reduces the replication of intermediates targeting the infection. [49]

As the mother's viral load increases, so does the risk of HBV perinatal transmission, which has been recorded as being as high as 28%. [44,52] This promotes the theory that the risk of perinatal transmission is reduced if the mother's viral load is also reduced at parturition, highlighting the potential of using antivirals. [44]

A number of studies have proposed that lamivudine can cause a rapid reduction of HBV DNA levels which is of particular importance in mothers with a high viral load. [21,53-56] This is supported by a number of studies which have shown significantly lower intrauterine HBV infection rates in women receiving this therapy. [21,47]

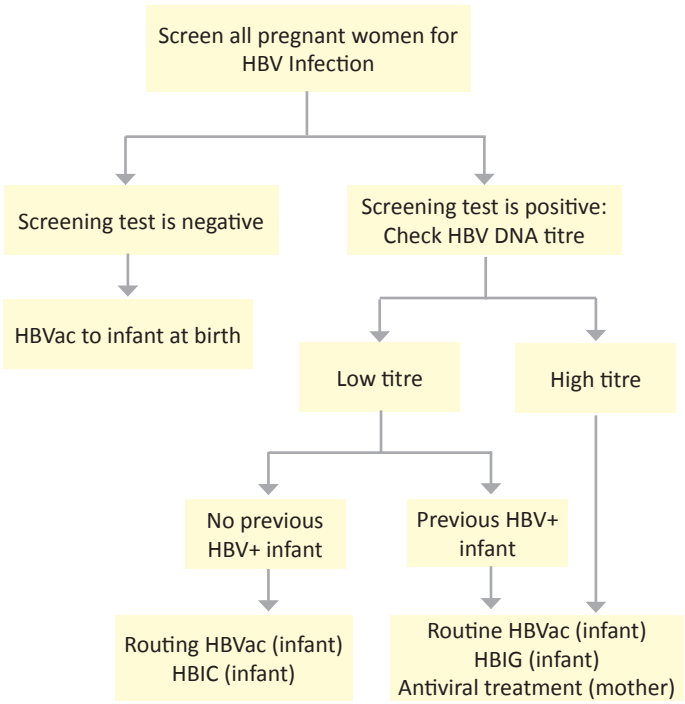


Figure 1. *Management of HBV infection during pregnancy*

As with all treatment regimes, both the risks and benefits must be considered before commencing therapy, despite the safety and efficacy of anti-viral agents such as lamivudine. Currently there is insufficient conclusive evidence relating to antiviral therapy to prevent HBV MTCT and thus, this treatment cannot be recommended at this time. [44] It is also to be noted that the mothers' liver disease status should be considered before commencing or continuing antiviral treatment. [21] The risks include the development of drug resistance in the mother and flares of hepatitis in the mother when the anti-viral drug is stopped in the postpartum period. The optimal timing of commencement and duration of use of these agents must also be determined.

Additional preventative measures

Topics under debate include associations between MTCT of HBV and bottle feeding or delivery methods such as caesarean section, in an attempt to inhibit the morbidity and mortality inflicted by this disease.

Breastfeeding

The literature is not clear as to whether breastfeeding should be avoided when the mother is hepatitis type B positive. This is a rather controversial topic as it is not known if HBV can be transmitted from mother to infant through breastmilk. [10]

Interestingly, studies have found that in HBV positive women who have breastfed, the rate of MTCT was lower than those who bottle-fed. [21,57,58] Conversely, other reports have found no difference in transmission rates among the two groups. [21,59]

It must be noted that HBV-infected mothers are advised against donating breastmilk and that breastfeeding is not recommended if the mother is taking antiviral medication. [21] This research has severe consequences for both the infant and community should bottle-feeding be recommended in these mothers.

Caesarean sections

As of yet, there is no hard evidence to argue whether delivery of the at-risk child should be via Caesarean section. [10]

Barriers to the delivery of preventative strategies

While the current preventative strategies are effective in inhibiting MTCT of HBV in the majority of cases, both developing and Western countries struggle to apply these methods in clinical practice. [38]

Developed countries

Developed countries have the economic stability and resources to successfully prevent the majority of cases of vertical HBV transmission. However, studies have shown that even in these countries, the recommended preventative strategies are not being carried out in every HBV infected mother. [38,44,60,61]

The US CDC states that 97% of American women undergo prenatal screening for HBsAg and that 92% of at-risk infants complete the full HBVac course by age three. [44] To the contrary, a 2010 study from the US found that although the proportion of mothers being screened for HBsAg was high, these rates were lower in certain ethnic and socioeconomic groups. Moreover, the study found that of the infants born to HBsAg-positive mothers, a mere 62.1% received the recommended prophylaxis within twelve hours of birth, with 13.7% receiving no HBVac whatsoever. It was concluded that having written hospital policy was the strongest predictor of HBVac administration. [38]

This is of significant concern. We now have the measures to prevent the majority of MTCT of HBV, yet health care facilities are failing to deliver this care. Not only are there gaps in policy making, but there are also gaps in policy implementation. Uniform protocols which are strictly adhered to are important for optimising prophylaxis rates. [38]

Developing countries

The main barriers against prevention in developing countries include cost, education and access. The cost of screening pregnant women is an extra expense, as is the cost of educating the community and local health workers. Access is also an obstacle in developing countries, with a high proportion of women receiving no antenatal care at all, let alone any specific to HBV. [62] These barriers are seemingly related to the economic and social issues these countries face.

The future of this research

There is a real deficit of information regarding disease prevention in infants not protected by the current prophylactic measures. The emerging prophylactic therapies, whilst seemingly promising, need to undergo larger rigorous clinical trials and safety audits.

Whilst vertical HBV transmission is a universal problem, the major burden is placed on developing countries. China is the exception. It seems that much of the cutting edge research relating to this topic from the last decade has come from China. This is positive for the future of HBV-infected mothers and their infants; as China becomes an increasingly larger economic player, solutions to these problems may be achieved. However, we also need to look at research in health care delivery. How do we improve compliance with protocol in this important area of disease prevention?

Conclusion

Vertical transmission of hepatitis B is a significant public health issue. It has been estimated that HBV infection is responsible for half of all cases of hepatocellular carcinoma and one third of liver cirrhosis. [3]

Currently the recommendations are to administer routine prophylaxis to the infants at risk, consisting of a completed course of HBVac and HBIG. This combination is highly effective in preventing perinatal transmission. [44] Despite the advances in prophylactic therapy, we are still faced with the harsh reality that up to 10% of infants are not effectively protected by this standard protocol and will still become

chronically infected. [16,42]

It should also be remembered that despite these advances in research and the current prophylactic recommendations, healthcare facilities are continuing to struggle with implementation. [38] The global community needs to work together to eradicate this disease. Inclusion of HBVac into national immunisation programs is estimated to prevent more than 80% of deaths relating to HBV alone. [20] Both governments and healthcare facilities need to contribute to gaps in policy making and implementation. [38]

Although countries such as the US and China are investing in research to uncover new and more effective means of prevention, there is still a considerable shortfall in the available literature. Uniform recommendations need to be set out as a standard for health care facilities to follow. In addition, there is a need for large scale studies to be performed so that the inconclusive information regarding the emerging preventative strategies can be resolved and vertical transmission can be effectively prevented, even amongst the highest risk groups.

Conflicts of Interest

None declared.

Correspondence

G Daley: gemma.daley@jcu.edu.au

References

[1] Ganem D, Prince A. Hepatitis B virus infection: Natural history and clinical consequences. N Engl J Med 2004;350(11):1118-29.
[2] Pungpapong S, Kim W, Poterucha J. Natural history of hepatitis B virus infection: An update for clinicians. Mayo Clin Proc 2007;82(8):967-75.
[3] Shepard C, Simard E, Finelli L, Fiore A, Bell B. Hepatitis B virus infection: Epidemiology and vaccination. Epidemiol Rev 2006;28(1):112-25.
[4] Anonymous. Hepatitis B vaccines. Wkly Epidemiol Rec 2004;79(28):255-63.
[5] Eke A, Eke U, Uchenna E. Hepatitis B immunoglobulin during pregnancy for the prevention of mother to child transmission of hepatitis B virus. Cochrane Database of Systematic Reviews 2010;(6).
[6] Rivkina A, Rybalov S. Chronic hepatitis B: Current and future treatment options. Pharmacotherapy 2002;22(6):721-37.
[7] Chen D. Toward elimination and eradication of hepatitis B. J Gastroenterol Hepatol 2009;25(1):19-25.
[8] Shi Z, Li X, Ma L, Yang Y. Hepatitis B immunoglobulin injection in pregnancy to interrupt hepatitis B virus mother-to-child transmission: A meta-analysis. Int J Infect Dis 2010;14(7):622-34.
[9] Hamdani-Belghiti S, Bouazzaou N. Mother-child transmission of hepatitis B virus. State of the problem and prevention. Arch Pediatr 2000;7(8):879-82.
[10] Guo Y, Liu J, Meng L, Meina H, Du Y. Survey of HBsAg-positive pregnant women and their infants regarding measures to prevent maternal-infantile transmission. BMC Infect Dis 2010;10:26.
[11] Cacciola I, Cerenzia G, Pollicino T, Squadrito G, Castellaneta S, Zanetti A, *et al.* Genomic heterogeneity of hepatitis B virus (HBV) and outcome of perinatal HBV infection. J Hepatol 2002; 36(3):426-32.
[12] Hyams K. Risks of chronicity following acute hepatitis B virus infection: A review. Clin Infect Dis 1995;20(4):992-1000.
[13] Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. Proc Biol Sci. 1993;253(1337):197-201.
[14] Vranckx R, Alisjahbana A, Meheus A. Hepatitis B virus vaccination and antenatal transmission of HBV markers to neonates. J Viral Hepat 1999;6(2):135-9.
[15] Zhang S, Yue Y, Bai G, Shi L, Jiang H. Mechanism of intrauterine infection of hepatitis B virus. World J Gastroenterol 2004;10(3):437-8.
[16] Lee C, Gong Y, Brok J, Boxall E, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: Systematic review and meta-analysis. BMJ 2006;332(7537):328-36.
[17] Noto H, Terao T, Ryou S, Hirose Y, Yoshida T, Ookubo H, *et al.* Combined passive and active immunoprophylaxis for preventing perinatal transmission of the hepatitis B virus carrier state in Shizuoka, Japan during 1980-1994. J Gastroenterol Hepatol 2003;18(8):943-9.
[18] Maddrey W. Hepatitis B: An important public health issue. J Med Virol 2000;61(3):362-6.
[19] Sangkomkamhang U, Lumbiganon P, Laopaiboon M. Hepatitis B vaccination during pregnancy for preventing infant infection. Cochrane Database of Systematic Reviews 2009;(3).
[20] Goldstein S, Zhou F, Hadler S, Bell B, Mast E, Margolis H. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol 2005;34(6):1329-39.
[21] Gambarin-Gelwan M. Hepatitis B in pregnancy. Clin Liver Dis 2007;11(4):945-63.
[22] Safary A, Beck J. Vaccination against hepatitis B: Current challenges for Asian countries and future directions. J Gastroenterol Hepatol 2000;15(4):396-401.
[23] Parkin D, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94(2):153-6.
[24] Zhang S, Han X, Yue Y. Relationship between HBV viremia level of pregnant women and intrauterine infection:neated PCR for detection of HBV DNA. World J Gastroenterol 1998;4(1):61-3.
[25] Ruff T, Gertig D, Otto B, Gust I, Sutanto A, Soewarso T, *et al.* Lombok Hepatitis B Model Immunization Project: Toward universal infant hepatitis B immunization in Indonesia. J Infect Dis 1995;171(2):290-6.
[26] Xu D, Yan Y, Choi B, Xu J, Men K, Zhang J, *et al.* Risk factors and mechanism of transplacental transmission of hepatitis B virus: A case-control study. J Med Virol 2002;67(1):20-6.
[27] Xu D, Yan Y, Xu J. A molecular epidemiology study on risk factors and mechanism of HBV intrauterine transmission. Chinese Med J 1999;79(1):24-7.
[28] Yin Y, Chen X, Li X, Hou H, Shi Z. Intrauterine HBV infection: Risk factors and impact of HBV DNA. J South Med Uni 2006;26(10):1452-4.
[29] Su H, Xu D, Li D, Zhang J, Lu J, Choi B. Heterogeneity analysis of the hepatitis B virus genome in intrauterine infection. J Med Virol 2005;77(2):180-7.
[30] Lopez M, Coll O. Chronic Viral Infections and Invasive Procedures: Risk of Vertical Transmission and Current Recommendations. Fetal Diagn Ther 2010;28(1):1-8.
[31] Ko T, Tseng L, Chang M, Chen D, Hsieh F, Chuang S, *et al.* Amniocentesis in mothers who are hepatitis B virus carriers does not expose the infant to an increased risk of hepatitis B virus infection. Arch Gynecol Obstet 1994;255(1):25-30.
[32] Grosheide P, Quartero H, Schalm S, Heijtink R, Christiaens G. Early invasive prenatal diagnosis in HBsAg-positive women. Prenat Diagn 1994;14(7):553-8.
[33] Alexander J, Ramus R, Jackson G, Sercely B, Wendel G. Risk of hepatitis B transmission after amniocentesis in chronic hepatitis B carriers. Infect Dis Obstet Gynecol 1999;7(6):283-6.
[34] Towers C, Asrat T, Rumney P. The presence of hepatitis B surface antigen and deoxyribonucleic acid in amniotic fluid and cord blood. Am J Obstet Gynecol 2001; 184(7):1514-8.
[35] Francis D, Favero M, Maynard J. Transmission of hepatitis B virus. Semin Liver Dis 1981;1(1):27-32.
[36] Assad S, Francis A. Over a decade of experience with a yeast recombinant hepatitis B vaccine. Vaccine 1999;18(1-2):57-67.
[37] Jackson Y, Chappuis F, Mezger N, Kanappa K, Loutan L. High immunogenicity of delayed third dose of hepatitis B vaccine in travellers. Vaccine 2007;25(17):3482-4.
[38] Willis B, Wortley P, Wang S, Jacques-Carroll L, Zhang F. Gaps in hospital policies and practices to prevent perinatal transmission of hepatitis B virus. Pediatrics 2010;125(4):704-11.
[39] Andre F, Zuckerman A. Review: Protective efficacy of hepatitis B vaccines in neonates. J Med Virol 1994;44(2):144-51.
[40] Mast E, Margolis H, Fiore A, Brink E, Goldstein S, Wang S, *et al.* A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: Immunization of infants, children, and adolescents. MMWR Recomm Rep 2005;54(16):1-31.
[41] Habib S, Shaikh O. Hepatitis B immune globulin. Drugs Today (Barc) 2007;43(6):379-94.
[42] Xiao X, Li A, Chen X, Zhu Y, Miao J. Prevention of vertical hepatitis B transmission by hepatitis B immunoglobulin in the third trimester of pregnancy. Int J Gynaecol Obstet 2007;96(3):167-70.
[43] Lee C, Gong Y, Brok J, Boxall E, Gluud C. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database of Systematic Reviews 2009;(2).
[44] Tran T. Management of hepatitis B in pregnancy: Weighing the options. Cleve Clin J Med 2009;76(Suppl 3):25-9.
[45] Beasley R, Hwang L, Lee G, Lan C, Roan C, Huang F, *et al.* Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet 1983;2(8359):1099-102.
[46] Bai H, Zhang L, Ma L, Dou X, Feng G, Zhao G. Relationship of hepatitis B virus infection of placental barrier and hepatitis B virus intra-uterine transmission mechanism. World J Gastroenterol 2007;13(26):3625-30.
[47] Li X, Yang Y, Hou H, Shi Z, Shen H, Teng B, *et al.* Interruption of HBV intrauterine transmission: A clinical study. World J Gastroenterol 2003;9(7):1501-3.
[48] Han Z, Zhong L, Wang J, Zhao Q, Sun Y, Li L, *et al.* The impact of antepartum injection of hepatitis B immunoglobulin on maternal serum HBV DNA and anti-HBs in the newborns. Chin J Int Med 2007;46(5):376-8.
[49] Shi Z, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: A systematic review and meta-analysis. Obstet Gynecol 2010;116(1):147-59.
[50] Johnson M, Moore K, Yuen G, Bye A, Pakes G. Clinical pharmacokinetics of lamivudine. Clin Pharmacokinet 1999;36(1):41-66.
[51] Zhu Q. Emphasis on the block of hepatitis B virus mother to infant transmission. Chin J Hepatol 2003;11(4):199-200.
[52] Huedo-Medina T, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006;11(2):193-206.
[53] Lai C, Chien R, Leung N, Chang T, Guan R, Tai D, *et al.* A one-year trial of lamivudine for chronic hepatitis B. N Engl J Med 1998;339(2):61-8.
[54] Kazim S, Wakil S, Khan L, Hasnain S, Sarin S. Vertical transmission of hepatitis B virus despite maternal lamivudine therapy. Lancet 2002;359(9316):1488-9.
[55] van Zonneveld M, van Nunen A, Niesters H, de Man R, Schalm S, Janssen H. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. J Viral Hepat 2003;10(4):294-7.
[56] van Nunen A, de Man R, Heijtink R, Niesters H, Schalm S. Lamivudine in the last 4 weeks of pregnancy to prevent perinatal transmission in highly viremic chronic hepatitis B patients. J Hepatol 2000;32(6):1040-1.

[57] Hill J, Sheffield J, Kim M, Alexander J, Sercely B, Wendel G. Risk of hepatitis B transmission in breast-fed infants of chronic hepatitis B carriers. Obstet Gynecol 2002;99(6):1049-52.
[58] Tseng R, Lam C, Tam J. Breastfeeding babies of HBsAg-positive mothers. Lancet 1988;2(8618):1032.
[59] Wang J, Zhu Q, Wang X. Breastfeeding does not pose any additional risk of immunoprophylaxis failure on infants of HBV carrier mothers. Int J Clin Pract 2003;57(2):100-2.
[60] Heininger U, Vaudaux B, Nidecker M, Pfister R, Posfay-Barbe K, Bachofner M, *et al.* Evaluation of the compliance with recommended procedures in newborns exposed to HBsAg-positive mothers: a multicenter collaborative study. Pediatr Infect Dis J 2010;29(3):248-50.
[61] Beckers K, Schaad U, Heininger U. Compliance with antenatal screening for hepatitis B surface antigen carrier status in pregnant women and consecutive procedures in exposed newborns. Eur J Pediatr 2004;163(11):654-7.
[62] Chen D. Public health measures to control hepatitis B virus infection in the developing countries of the Asia-Pacific region. J Gastroenterol Hepatol 2000;15 Suppl:E7-10.