Chronic hepatitis B in Asian women of childbearing age

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Received: 13 March 2009 / Revised: 5 June 2009 / Accepted: 17 June 2009 / Published online: 9 July 2009
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Abstract Hepatitis B virus (HBV) infection is a serious clinical problem affecting approximately 2 billion people worldwide. An estimated 350 million live with chronic hepatitis B (CHB) infection and are at an increased risk for serious liver sequelae and death from acute or chronic consequences of CHB infection. Individuals with CHB have a 20–30% risk of early death from complications, including liver cirrhosis and hepatocellular carcinoma. In the Asia-Pacific region, half of the CHB burden results from vertical or mother-to-child transmission, with early childhood horizontal transmission accounting for the remaining half. Screening and vaccination are key factors in the successful prevention and control of HBV infection. Over the last 20 years, the implementation of screening programs and universal HBV vaccination for all individuals born in endemic areas have reduced the prevalence of HBV infection and HBV-related liver diseases among individuals younger than 30 years. Women of childbearing age are key stakeholders in preventing HBV infection and, as such, play a critical role in reducing the vertical and horizontal transmission of HBV. Further efforts are needed to implement screening and educational programs for women of childbearing age, particularly those with CHB, to prevent the transmission of HBV to newborns, spouses, other household members, and sexual partners. In addition, healthcare workers need to learn how to avoid iatrogenic transmission in the healthcare setting. This article reviews

these issues and highlights areas in which their engagement with public health efforts serves to improve quality of life and society as a whole.

Keywords Chronic hepatitis B · Women of childbearing age · Hepatitis B virus · Pregnancy

Introduction

Hepatitis B virus (HBV) infection remains a serious clinical problem because of its worldwide distribution and potential, adverse liver-related sequelae. HBV and chronic hepatitis B (CHB) are endemic in the Asia-Pacific region, where they are leading causes of serious liver morbidity and mortality. The prevalence of HBV serologic markers indicates the HBV infection status in the specific populations studied. Hepatitis B surface antigen (HBsAg) is a serologic marker of infection and can be detected during chronic and acute hepatitis B infection; antibody to hepatitis B surface antigen (anti-HBs) is a marker of immunity from exposure to HBV or HBV vaccine; and immunoglobulin G (IgG) antibody to core hepatitis B antigen (anti-HBc) is a marker of exposure to HBV and is detectable in individuals with acute hepatitis B, CHB, or past HBV infection. Generally speaking, HBsAg seroprevalence usually reflects the presence of CHB in a given population. The rate of HBV infection is estimated to be 36–57% and HBsAg prevalence ranges from 3.8 to 16.8% in Mainland China, with higher rates observed in rural areas [1]. The seroprevalence of HBsAg among adults in other Asian countries has remained similar over the past two decades, ranging from 2 to 20% [2–13]. CHB runs an insidious and often progressive course and, when left untreated, can lead to cirrhosis, decompensated liver disease, and

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hepatocellular carcinoma (HCC) [14]. The associated morbidity, mortality, and medical health expenditure are immense. Complications usually start to manifest in adulthood, often in the prime of an individual's life, and often result in much personal and social distress.

Most Asians with CHB are infected at birth or in early infancy by CHB-infected mothers [15, 16]. The risk of intrauterine infection is relatively low because the fetus is protected from HBV by the placenta. Horizontal transmission from fathers, siblings, and playmates with CHB is a significant factor. Early infant infection seldom manifests as symptomatic acute hepatitis but evolves to chronic infection. Evidence from long-term follow-up studies on the impact of the implementation of universal HBV vaccination programs in Taiwan has clearly demonstrated that the prevention of mother-to-child transmission is the mainstay for the control of HBV infection in the Asia-Pacific region [17–20].

CHB seldom causes specific symptoms. Serostatus can be established only by blood tests for HBsAg, infectivity can be established by blood tests for HBV DNA, and the presence of disease can be established by regular monitoring with blood tests and liver imaging. Without therapeutic intervention, at least 30% of individuals with CHB will develop significant disease [21]. The interaction of the host immune system and the virus determines the outcome and the natural course of disease, which consists of 3 phases: the immune-tolerant, immune clearance, and inactive residual phases [22]. The immune-tolerant phase, when the host immune system does not react to active viral replication, is characterized by the presence of hepatitis B e antigen (HBeAg), high serum HBV DNA levels (at least 2×10^9 copies/ml), normal alanine aminotransferase (ALT) levels, and an absence of hepatitis activity. After a variable duration, the individual enters the immune clearance phase, when host immune reaction to HBV is characterized by a reduction in serum HBV DNA levels, intermittent acute ALT flares that can exceed 5 times the upper limit of normal (ULN), and evidence of active hepatitis upon liver biopsy. The loss of HBeAg and the appearance of antibody to hepatitis B e antigen (anti-HBe), referred to as HBeAg seroconversion, mark the transition to the inactive residual phase, which is followed by a reduction in serum HBV DNA levels, sometimes beyond the limit of detectability, and the clinical remission of liver disease. Women with CHB generally have a better prognosis and go through the first two phases of the disease (i.e., the immune-tolerance and immune clearance phases) to the third, inactive, phase. However, some will progress to HBeAg-negative CHB [23, 24]. Individuals with active viral replication are capable of transmitting the infection. Most individuals with CHB remain HBsAg positive throughout their lives due to the persistence of

very low-grade HBV infection. Only a small percentage ($\sim 0.5\%$) of patients with CHB may lose HBsAg and even undergo HBsAg seroconversion.

Prevalence of CHB among Asian women of childbearing age

Data from the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), the Red Cross Blood Donation Service, local healthcare agencies, and independent research groups that monitor the epidemiology of HBV infection in Asian countries have shown a trend toward decreasing infection in the majority of these countries. The seroprevalence of HBsAg is generally lower in women than in men. Before the introduction of the HBV vaccine during the 1980s, the male-to-female ratio was 1.4:1 in China, 1.3:1 in Thailand, and 1.1:1 in Hong Kong. One-third of the 3 million individuals infected annually come from China. A national seroepidemiologic survey in 2002 showed that 10–12% of the adult population and 5% of children younger than 5 years were HBsAg positive. Taiwan also has a high rate of HBsAg seroprevalence (10–14%) among its adult population, whereas prevalence rates in the Philippines are 2–16.5%, Vietnam and Thailand 14%, and Southeast Asia, Japan, Korea, and India at a more modest 2–5% [2, 3, 6, 7, 9, 11, 13]. In many developing countries, HBsAg seroprevalence also differs between urban and rural areas. In Vietnam, seroprevalence is as high as 20% in the rural Thanh Ho province, but only 10% in Ho Chi Minh City. In China, on the other hand, HBsAg prevalence is 10.1% in rural areas and 8.8% in urban areas. HBsAg seroprevalence varies among different ethnic groups. It has been reported to be 13.8% among the Hmong and Lahu tribes compared with 22.6% among the general population in northern Thailand. Similarly, HBsAg seroprevalence was 17% among the aboriginal Fukien and Hakka populations in Taiwan compared with a prevalence of 26% among the general population [4, 5, 8, 10, 12]. The reason for these differences may be related to the high endemicity carried down from one generation to the next by vertical transmission as well as horizontal transmission.

Epidemiologic reviews indicate that Asian patients generally undergo HBeAg seroconversion at a median age of 35 years. Viral clearance occurs at an estimated annual incidence of 2–15% [25, 26]. In a cross-sectional analysis of 544 women, aged 18–50 years, with CHB, who were followed in a district hospital in Hong Kong, 38.4% were HBeAg positive and 61.6% were HBeAg negative [27]. In the younger cohort (18–30 years of age), the HBeAg positivity rate was higher at 50.3%. Serum HBV DNA levels

were more than 8 log₁₀ copies/ml in 55.6% of the patients; none had HBV DNA levels less than 2 log₁₀ copies/ml. Among patients aged 31–40 years, the HBeAg positivity rate was 34.9%, with 53.8% of patients having HBV DNA levels of more than 8 log₁₀ copies/ml. This demonstrates the higher risk of vertical and horizontal mother-to-child transmission in younger mothers [27]. These data can help facilitate a healthcare strategy, but the severity of liver disease in these women needs to be assessed on an individual basis.

CHB in women and its effect on pregnancy

Women with CHB generally undergo earlier HBeAg seroconversion and enter the quiescent phase sooner than do their male counterparts. Some women may have progressed to the phase of inactive disease or phase of HBeAg-negative active CHB [28]. This observation has stimulated much research interest in the role and influence of sex hormones on the host immune interaction with HBV. Hormonal changes during pregnancy enhance the immune clearance of HBV [29, 30].

A Swedish retrospective study showed that serum HBV DNA levels increased by a mean of 0.4 log₁₀ copies/ml late in pregnancy and during the early postpartum period. Even in HBeAg-negative mothers, serum HBV DNA levels increased in 25% of the patients by more than 1 log₁₀ copies/ml during pregnancy. Elevations in ALT levels occurred in both HBeAg-positive and HBeAg-negative women in late pregnancy and immediately postpartum [31, 32]. The incidence of fulminant hepatitis is increased in pregnant women with CHB, especially in the last trimester, compared with nonpregnant women and men with CHB. In a review of 35 mothers with CHB in Singapore, 75% were unaware that they were infected [33]. In these patients, HBsAg-positive status was documented for the first time at an antenatal registry when they were in their second trimester. Of this group, 66% were HBeAg positive and just over 50% had elevated ALT levels. Loss of HBeAg during pregnancy was significantly higher in these patients than in controls ($P = 0.002$). No hepatic decompensation was recorded in this cohort.

Some women of childbearing age may have advanced disease that reduces fertility. The risk of complications during vaginal delivery in patients with cirrhosis and portal hypertension can be reduced by elective cesarean delivery. A telephone interview survey by the Chinese University of Hong Kong showed that many women were worried about their infection adversely affecting their health and damaging their offspring. Many decided not to get pregnant because of erroneous information.

Antiviral treatment options for CHB in women of childbearing age and during pregnancy

Clinical experience is limited with regard to the management of CHB in women of childbearing age and during pregnancy. Currently, there is no gold standard for CHB treatment in this population. Recently, treatment guidelines for CHB published by the Asian Pacific Association for the Study of the Liver recommended interferon (IFN)-based therapy for the treatment of nonpregnant women of childbearing age who have CHB [34]. However, IFN-based therapy is contraindicated in women who are pregnant or plan to become pregnant because of its antiproliferative/teratogenic effect. Oral nucleos(t)ide analogs (NAs) may be considered for therapy, but among these agents only telbivudine and tenofovir are classified as category B drugs (i.e., demonstrating no risk in animal studies, but of unknown risk in humans), whereas lamivudine, adefovir, and entecavir are classified as category C drugs (i.e., teratogenic in animal studies, but of unknown risk in humans) by the US Food and Drug Administration [35]. Tenofovir treatment during pregnancy in women infected with the human immunodeficiency virus (HIV) is associated with a low rate of birth defects, particularly when it is given in the second and third trimesters (Table 1). Before selecting treatment, it is important to consider the stage of the mother's liver disease and potential benefit of treatment in relation to the potential risk to the fetus. Women of childbearing age should consider delaying pregnancy and receiving pegylated IFN (PEG-IFN) therapy first, especially if their serum ALT levels are 2–5 times the ULN. If their ALT level is less than 2 times the ULN and/or they have compensated cirrhosis, they should consider pregnancy first and begin treatment after the infant is born. This strategy is feasible in most families that plan for 1 or 2 offspring but may be difficult if a large family is planned. The physician must have an open and detailed discussion to help the women and their families reach the best decision. For women who become pregnant while receiving oral NA therapy, current guidelines recommend continuing treatment if the drug is a category B drug such as telbivudine and tenofovir [34]. Emerging evidence suggests that the use of lamivudine in the last month of pregnancy might prevent mother-to-infant transmission of HBV in women with high HBV DNA levels [36–40].

One recent study assessed the effect of lamivudine therapy during pregnancy in 150 highly viremic pregnant women who were randomized to receive lamivudine 100 mg or placebo, from week 32 of gestation to week 4 postpartum [36]. After birth, infants from lamivudine-treated mothers were treated immunoprophylactically with lamivudine, HBV vaccine, and hepatitis B immunoglobulin (HBIG) ($n = 56$) or lamivudine and HBV vaccine

Table 1 Birth defect rate by trimester of earliest exposure: comparison of exposure to tenofovir regimen and exposure to all antiretrovirus regimen in patients with HIV infection

Trimester	Parameter	Tenofovir regimen	All antiretroviral regimen
First	Defects/live births	14/606	126/4,326
	Prevalence (95% CI)	2.3% (1.3–3.9)	2.9% (2.4–3.5)
Second/third	Defects/live births	5/336	145/5,618
	Prevalence (95% CI)	1.5% (0.5–3.4)	2.6% (2.2–3.0)

CI confidence interval

($n = 26$), whereas infants from placebo-treated mothers received placebo, HBV vaccine, and HBIG ($n = 59$). There were no maternal or fetal safety issues observed in any of the treatment arms. Efficacy results showed that lamivudine reduced HBV transmission from mothers to infants who received passive-active immunization, as measured by a decrease in the incidence of HBsAg seropositivity and in detectable HBV DNA levels. Although the results from this study are positive, questions have been raised regarding the extent of benefit, the maternal threshold serum HBV DNA level required for initiating therapy, the optimal initiation and duration of therapy, and the appropriate choice of therapy [41].

Women's role in the prevention of HBV transmission

Prevention of mother-to-child transmission

The prevention of vertical transmission from CHB-infected mothers to their children reduces HBV-related mortality in the long run. This can be achieved by the universal vaccination of newborns in endemic areas. Plasma-derived vaccines used in the 1980s were effective, but there were unsubstantiated concerns of transmission of HIV infection. Recombinant vaccines were then introduced; these were safe, effective, and affordable. The implementation of mass immunization programs recommended by the WHO since 1991 has decreased the incidence of HBV infection among infants, children, and adolescents in many countries. The advances in the prevention of HBV transmission have yielded encouraging results. Taiwan introduced an HBV vaccination program in 1988, and HBIG was additionally given to infants of HBeAg-positive mothers [20, 42, 43]. In 2004, a survey showed seropositive rates for HBsAg, anti-HBs, and anti-HBc of 1.2, 50.5, and 3.7%, respectively, in individuals born since the introduction of the vaccination program (i.e., individuals younger than 20 years). Individuals positive for HBsAg were born mostly to HBsAg-positive mothers. In the actively followed cohort, no increased incidence of CHB was found. Vaccination reduces both vertical and horizontal transmission.

The incidence of liver cancer among children has also been reduced significantly. In a long-term study involving 318 children in Hong Kong, which sought to evaluate the immunogenicity and efficacy of different regimens of HBV vaccination, no patients were found to be HBsAg positive during the 22 years of follow-up and 72 of 317 patients had at least 1 episode of amnesic response (i.e., rapid and more pronounced production of anti-HBs upon second encounter with HBsAg antigen) [44].

However, many endemic countries have not been able to provide good coverage to their citizens. Recombinant HBV vaccines are still relatively expensive, and there are no efficient and dedicated healthcare systems to deliver the important first dose to infants within 24 h of birth. Lack of knowledge among mothers, compounded by a lack of commitment from the healthcare providers, creates major barriers to improvement. In response to this, the Global Alliance for Vaccines and Immunization plan was established by the WHO. This has dramatically increased access to vaccines in poor countries, such as Cambodia, China, the Lao People's Democratic Republic, and Vietnam. In 2002, the WHO Working Group met in Tokyo and reiterated its immunization strategies. These include plans to ensure quality of routine immunization services, especially coverage, injection safety, universal infant immunization with a high-risk approach that focuses on protecting the infants of HBV-infected mothers, timely delivery of a birth dose (within 24 h of birth), and the addition of vaccine vial monitors in remote areas facilitated by UNICEF-procured vaccines. As part of the expanded program on immunization developed by the WHO in conjunction with UNICEF and a coalition of partners, the regional milestones used to monitor the progress of HBV control included at least 80% full immunization (receipt of three doses of HBV vaccine), a system to monitor the timeliness of birth doses by 2004, the achievement of HBsAg seroprevalence of less than 1% in individuals born after routine vaccination started, and the establishment of a hepatitis B control plan that includes a protocol to monitor healthcare worker knowledge. Currently, all countries in the Asia-Pacific region except the Philippines, India, and Cambodia have implemented universal infant immunization programs. Data from UNICEF

from 2005 indicated that HBV vaccine coverage in infants ranged from 70 to 90% in most Asia-Pacific countries [45]. Unfortunately, the implementation of vaccination programs is reportedly inconsistent and access to these programs remains limited in some countries such as Myanmar, Bangladesh, and India as well as some rural areas, such as remote areas of China, where coverage is only 29% [2, 6, 13, 45, 46] (Table 2). Vaccine failure leading to vertical transmission remains a challenge. This may be reduced by administering HBIG to infants whose mothers are HBeAg positive or have high serum levels of HBV DNA.

A review of the response to HBV vaccination among newborns has shown that 7–10% of nonresponders or insufficient responders have anti-HBs levels of less than 10 IU/l. A number of possibilities account for poor response to HBV vaccination. These include intrauterine infection, vaccine escape mutants, host genetic hyporesponsiveness or nonresponsiveness to HBsAg, and immune compromise.

The proposal to use oral antiviral agents to reduce maternal HBV DNA serum levels in the third trimester and immediate postnatal period to avoid mother-to-newborn transmission was evaluated in a pilot study using antiviral therapy, such as lamivudine, in the third trimester to reduce maternal serum HBV DNA level by the time of birth [37]. However, the trial did not yield convincing efficacy results. One (12.5%) of the eight offspring of highly viremic mothers receiving lamivudine 150 mg still became infected and had CHB, compared

with 28% of historic controls who did not receive lamivudine therapy. Thus, the administration of oral antiviral therapy in the third trimester to women with CHB is controversial because there is no evidence to confirm a significant reduction in infection rates among infants and, more important, the safety of antiviral therapy in pregnant women is unproven. Withdrawal flare after delivery is an additional safety concern [37]. Antiviral therapy may not be available for mothers with CHB in developing regions where there is no healthcare system to oversee the administration of complicated management regimens.

Mathematical models have been used to project disease trends and the impact of HBV vaccination on disease outcome. In Vietnam, the prevalence of CHB among men and women was estimated on the basis of age-specific HBV prevalence from Vietnamese community-based studies. Universal infant HBV vaccination from 2003 was assumed to reduce HBV infection by 90% in subsequent birth cohorts. Over the next two decades, universal infant HBV vaccination is expected to reduce chronic HBV prevalence in Vietnam, from 8.4 million cases in 2005 to 8.0 million cases by 2025. However, the HBV-related liver disease burden from cirrhosis and HCC will continue to rise on the basis of the estimated incidence with HBV DNA levels from the Taiwanese Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer in HBV (REVEAL-HBV) study [47, 48]. Estimated HBV-related mortality is expected to increase from 12,600 in 1990 to

Table 2 Demographic and health statistics for children living in the Asia-Pacific region in 2006

Country	Life expectancy (year)	Urbanized population in 2006 (%)	Contraceptive users (%)	Antenatal care coverage (%)	Skilled attendant at delivery (%)	Institutional deliveries (%)	Lifetime risk of maternal death (1 in ...)	One-year-olds immune to HBV (%)	Mothers not breast-feeding (%)
Bangladesh	63	25	58	48	20	16	51	88	37
Cambodia	59	20	40	69	44	22	48	80	60
China	73	41	87	90	98	83	1,300	91	51
India	64	29	56	74	47	41	300	6	6
Indonesia	70	49	57	92	72	40	97	70	40
Japan	82	66	56	NA	100	NA	11,600	NA	NA
Korea	67/78	62/81	62/81	NA/NA	97/100	NA/NA	140/6,100	96/99	65
Lao People's Democratic Republic	64	21	32	27	19	NA	33	57	57
Malaysia	74	68	55	79	98	98	560	87	87
Myanmar	61	31	34	76	57	16	110	75	75
Pakistan	65	35	28	36	31	28	74	83	83
Philippines	71	63	49	88	60	38	140	27	88
Thailand	70	33	77	98	92	97	500	96	96
Vietnam	74	27	76	91	88	64	280	93	93

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40,000 in 2025 [49]. A national HBV strategy is required to address this expanding burden of liver disease.

Prevention of horizontal transmission of HBV

HBV can be transmitted through sexual intercourse, close social contact, and parenteral exposure. CHB-infected women of childbearing age may transmit HBV infection to their sexual partners, other household members, and occupational contacts, especially if they work in the healthcare setting. Unfortunately, health knowledge and hygiene tend to be low in many parts of the Asia-Pacific region, and health policy in general does not address these issues thoroughly. Many CHB-infected individuals are not aware of their HBV status and transmit the infection unknowingly.

Sexual transmission may not add to the chronicity burden but can result in acute hepatitis B. Women with CHB may infect their nonimmunized partners if safe sex is not practiced. Professional sex workers are at risk of acquiring and transmitting HBV and other sexually transmitted diseases [50].

Immigration from the East to the West introduces Asian populations with a higher prevalence of CHB to areas in which most individuals are not immune to hepatitis B. This has the potential to increase the incidence of acute hepatitis B [51, 52]. Recently, the Centers for Disease Control and Prevention (CDC) published updated and expanded guidelines for HBsAg testing and new recommendations for public health evaluation and management for persons with chronic infection and their contacts [53]. Routine testing for HBsAg now is recommended for additional populations with an HBsAg prevalence of 2% or more: persons born in geographic regions with an HBsAg prevalence of 2% or more, men who have sex with men, and injection drug users [53]. The CDC guidelines serve as a resource on the management of HBV infection for public health officials, organizations, and healthcare professionals involved in the development, delivery, and evaluation of the prevention of HBV.

In many Asian countries, women constitute the majority of the healthcare workforce. As a result, there are woman physicians and surgeons, nurses, and healthcare assistants who suffer from CHB. The occupational risk of healthcare workers transmitting HBV infection to their patients has been well documented in the past. Health authorities in the United States, Canada, and the European Union have issued guidelines for healthcare workers who have CHB to prevent infecting patients through open wounds, medical interventions, or surgery. Different guidelines exist for the management of HBV-infected healthcare workers. Various HBV DNA levels are used as cutoff points to determine whether an HBV-infected healthcare worker will be

allowed to perform exposure-prone procedures (EPPs). If the level of HBV DNA in the serum is used to determine acceptability for the conduct of EPPs, it is necessary to take into account the variability of HBV DNA levels over time in HBV carriers and the reliability and reproducibility of the molecular diagnostic test involved. The issue of standardization has to be addressed before a universal, maximum level of viremia for healthcare workers performing EPPs can be introduced [54]. Currently, there are no strict guidelines in Asian countries to prevent CHB-infected female healthcare workers from being employed in fields that involve patient contact and open-wound care. The prevention of transmission relies on universal precautions.

Conclusion

CHB is still endemic in many countries in the Asia-Pacific region, and the healthcare burden will continue to rise. Looking ahead, the healthcare costs for CHB-related disease should decline over time because serious complications are now avoidable with effective therapy. In addition, the impact of universal vaccination programs for HBV should alleviate the vicious cycle of vertical transmission and high chance of chronicity. The success of these strategies requires the dedication of local and national health authorities to provide appropriate resources and vaccines. Better health education for women of childbearing age will also help ensure better antenatal care.

Acknowledgment Editorial support in the development of the manuscript was provided by Kathleen Covino, PhD. This study has been supported by an independent educational grant from Bristol-Myers Squibb Company through the ACT-HBV Initiative.

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