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GUIDELINES

Asian Pacific association for the study of liver (APASL) guidelines: hepatitis B virus in pregnancy

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Abstract
Hepatitis B virus (HBV) infection still remains a major public health issue in the Asia–Pacific region. Most of the burden of HBV-related disease results from infections acquired in infancy through perinatal or early childhood exposure to HBV in Asia–Pacific. Hepatitis B during pregnancy presents unique management issues for both the mother and fetus. These APASL guidelines provide a comprehensive review and recommendations based on available evidence in the literature, for the management of females with HBV infection through every stage of pregnancy and postpartum. These also address the concerns, management challenges, and required follow-up of children born to hepatitis B-positive mothers.

Keywords Hepatitis B · Acute Hepatitis B · Chronic Hepatitis B · Pregnancy

Introduction

Despite the availability of effective preventive measures including vaccination, hepatitis B virus (HBV) infection is still today a major public health issue worldwide, especially in the Asia–Pacific region. Chronic HBV infection may progress to hepatic decompensation, hepatocellular carcinoma, and cirrhosis.

Hepatitis B during pregnancy presents unique management issues for both the mother and the fetus.

Mother-to-child transmission (MTCT) is responsible for a majority of prevalent cases of chronic HBV infection in the Asia–Pacific region. Because HBV infection in infancy or early childhood often leads to chronic infection, it is important to take appropriate measures to prevent MTCT.

These guidelines are intended to be used by health-care providers, and suggest the preferred approaches to the management of females with HBV infection throughout the pregnancy and the postpartum period, and of children born to infected mothers. This document provides general guidelines only and will be applicable to the management of most of the patients, but should not replace clinical judgment for unique patients. In addition, despite increasing knowledge and research, some areas of uncertainty still exist and, therefore, appropriate choices should be made based on the evolving evidence, and the current literature as it evolves.

The experts from the members of the APASL guidelines' development sub-committee were given specific areas for reviewing and writing consensus statements according to the level of evidence and strength of recommendation as per the current literature (Table 1) [1]. Then, the manuscript was circulated to all the members of the group for suggestions and endorsement.

Epidemiology of hepatitis B virus infection in pregnant females in Asia–Pacific

Review of literature

The burden of HBV infection in the general population including pregnant females is particularly high in

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the Asia–Pacific region, although it varies widely among countries. The common routes of transmission of HBV are perinatal transmission; and horizontal transmission (during childhood through close contacts, unsafe injection practices, and transfusion of blood products) [2].

In the Asia–Pacific, most of the burden of HBV-related diseases results from infections acquired in infancy through perinatal or early childhood exposure to HBV. Infection acquired at an early age commonly becomes chronic: the rates of development of chronicity for infants infected in the first year of life, for children infected between 1 and 5 years of age, and peoples infected as adults are 80–90%, 30–50%, and < 5%, respectively [3].

The World Health Organization (WHO) Global Health Sector Strategy on Viral Hepatitis 2016–2021 had defined targets for elimination of viral hepatitis as a major global public health threat by 2030 [4]. All WHO regions are working toward the 2030 global hepatitis B elimination target of a 90% reduction in new cases of chronic HBV infection (equivalent to < 0.1% HBsAg prevalence among children aged 5 years). Other global targets for 2030 include 90% coverage of hepatitis B vaccine birth dose (within 24 h) (HepB birth dose vaccination) and other interventions to prevent MTCT of HBV, and 90% coverage of all doses of HBV vaccine (HepB3) [4].

For the purpose of reviewing the epidemiology in the Asia–Pacific region, the countries of the region were grouped as follows (according to geography): North Asia (Russia); Central Asia (Afghanistan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan); Western Asia (Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iran, Iraq, Israel, Palestine, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, Yemen);East Asia (China Mainland, Mongolia, North Korea, South Korea, Japan, Taiwan); Southeast Asia (Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, Vietnam); South Asia (Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Sri Lanka); and Pacific Countries (Australia, New Zealand, and Pacific Island Countries and Territories). Pacific Island Countries and Territories include Samoa, Bougainville, Cook Islands, Federated States of Micronesia, Fiji, French Polynesia, Guam, Kiribati, Nauru, New Caledonia, Papua New Guinea, Samoa, Solomon Islands, Tokelau Islands, Tonga, Tuvalu, Vanuatu, and Wallis and Futuna Islands.

North Asia (Russia)

In Russia, all pregnant females are tested for HBsAg in the first and in the third trimesters of pregnancy. Nevertheless, the data on the prevalence of chronic HBV infection in this population group are accessible only in some regions, since there is no general registration of this data. The modeled HBsAg national and children under-5-year-old prevalence in 2019 were estimated to be 0.6% (95% CI 0.54–0.67%) and 0.03% (0.03–0.04%), respectively [5] (Table 2). In 2019, Russia achieved HepB3 coverage of 97% [6] (Table 2).

The available studies show that the prevalence of chronic HBV infection in pregnant females varies significantly depending on the region of Russia and the year the study was conducted. For example, HBsAg prevalence among pregnant female in Russia was reported as 0.7% in 2014 and 0.5% in 2015 [7]. Note that these data include all forms of hepatitis B, i.e., acute hepatitis B, as well as chronic HBV infection. The HBsAg detection rate in pregnant females also varies significantly across regions of Russia. In northern and central regions, the prevalence of HBsAg in pregnant females varies between 0.3 and 0.5%, while in south-eastern and eastern parts of the country, it reaches 1.4–1.5% [8–10].

Central Asia (Afghanistan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan)

There are little data on HBV infection in pregnant females from Central Asian countries. The modeled HBsAg national and children under-5-year-old prevalence in 2019 were estimated to be 5.9% (95% CI 4.63–7.17%) and 1.66% (1.16–2.2%) in Afghanistan, 2.26% (1.85–2.57%) and 0.22% (0.17–0.28%) in Kazakhstan, 2.55% (2.13–2.99%) and 0.64% (0.50–0.81%) in Kyrgyzstan, 2.52% (2.11–2.89%) and 0.29% (0.22–0.37%) in Tajikistan, 2.65% (2.23–3.02%) and 0.38% (0.28–0.46%) in Turkmenistan, and 4.34% (3.85–4.9%) and 0.42% (0.29–0.52%) in Uzbekistan, respectively [5]. In 2019, HepB3/HepB-birth dose coverage was 66%/37% in Afghanistan, 97%/93% in Kazakhstan, 95%/ 96% in Kyrgyzstan, 97%/99% in Tajikistan, 99%/99% in Turkmenistan, and 96%/99% in Uzbekistan, respectively [6].

While a low HBsAg prevalence in pregnant females has been reported from Afghanistan (1.14% in 2010) [11] and Kazakhstan (1.2% in 2016) [12], a much higher prevalence of 10.1% (in 2015) is reported from Tajikistan (however, the reliability of these data is questionable due to a small size of the considered group) [13]. There are no data regarding HBsAg positivity among pregnant females in Uzbekistan, Kyrgyzstan, and Turkmenistan.

Western Asia (Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, and Yemen)

There are little data on HBV infection in pregnant females from Western Asian countries. The modeled HBsAg national and children under-5-year-old prevalence in 2019 were estimated to be 2.09% (95% CI 1.72–2.37%) and

Table 1 Evidence grade used for the APASL Guidelines on Hepatitis B in pregnancy (adapted from the GRADE system [1]

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate Effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect. Any estimate of effect is uncertain	C
Grading of recommendations	**Notes**	**Symbol**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	2

0.16% (0.11–0.21%) in Armenia, 3.22% (2.79–3.63%) and 0.56% (0.41–0.72%) in Azerbaijan, 2.64% (2.25–3.03%) and 0.12% (0.09–0.16%) in Bahrain, 0.7% (0.67–0.72%) and 0.02% (0.01–0.02%) in Cyprus, 1.48% (1.46–1.5%) and 0.24% (0.21–0.28%) in Georgia, 1.53% (1.34–1.71%) and 0.09% (0.07–0.11%) in Iran, 1.98% (1.62–2.31%) and 0.43%(0.31–0.56%) in Iraq, 0.53% (0.43–0.62%) and 0.04% (0.02–0.05%) in Israel, 3.37% (3.26–3.48%) and 0.53% (0.50–0.56%) in Jordan, 1.17% (0.97–1.41%) and 0.07% (0.05–0.09%) in Kuwait, 2.82% (2.43–3.24%) and 0.58% (0.43–0.76%) in Lebanon, 2.5% (2.11–2.9%) and 0.09% (0.07–0.11%) in Oman, 1.4% (1.25–1.55%) and 0.10%(0.07–0.13%) in Qatar, 2.72% (2.31–3.14%) and 0.15% (0.12–0.19%) in Saudi Arabia, 3.08% (2.99–3.17%) and 0.82% (0.67–0.96%) in Syria, 2.43% (2.31–2.56%) and 0.17% (0.14–0.20%) in Turkey, 1.82% (1.51–2.11%) and 0.12% (0.09–0.17%) in United Arab Emirates, and 5.46% (4.93–6.0%) and 1.63% (1.28–2.01%) in Yemen respectively [5].

In 2019, HepB3/HepB-birth dose coverage was 92%/96% in Armenia, 94%/98% in Azerbaijan, 99%/98% in Bahrain, 94%/94% in Georgia, 99%/95% in Iran, 84%/41% in Iraq, 96%/95% in Israel, 91%/93% in Kuwait, 80%/80% in Lebanon, 99%/99% in Oman, 98%/ 97% in Qatar, 97%/96% in Saudi Arabia, 99%/99% in Turkey, and 98%/91% in United Arab Emirates, respectively [6].The HepB3 coverage in 2019 was 94% in Cyprus, 89% in Jordan, 54% in Syria, and 73% in Yemen, respectively [6].

An old report found HBsAg prevalence of 0.2% in 1998 and 0.5% in 1999, in pregnant females in Armenia [14]. In Armenia, coverage of infant vaccination and three doses of Hepatitis B universal vaccination is increasing gradually. As a result, incidence of Hepatitis B has been dramatically decreased among the children under 14 years old since introduction year in 1999 [15].

In Azerbaijan, 1.5% HBsAg positivity was found in 2010 in pregnant females [16].

In Iran, HBsAg prevalence in pregnant females range from 1.3% in 2014 to 0.18% in 2016 [16–26] (Table 2). In a recent meta-analysis published in 2018, the pooled prevalence of HBsAg among pregnant females was 1.35% (95% CI 1.22–1.48%) in Iran [27].

In Iraq, a case–control study done in Baghdad on 40 pregnant females visiting private-sector hospital in 2010–2011 showed HBsAg to be 5% [28]. However, another study done in primary health centers on 6975 pregnant females in 2016–2017 found HBsAg prevalence to be 0.13% [29].

Reported HBsAg prevalence in pregnant females in Israel, in a review in 1999, was ranging from 0.6 to 4% with rates varying among ethnic groups [30]. In a study published in 2010, on 186 619 deliveries from 1988 to 2007, at a University medical center, found HBsAg prevalence of 0.3% [31]. Another study on all singleton deliveries between the years 1991–2014 at a University Medical Center in Israel found 0.2% HBsAg prevalence in pregnant females [32].

Reported prevalence among pregnant females in Jordan ranges from 4.3 in 2002 to 5% in 2020 [33, 34].

A study done in 2012–2013 in 4062 pregnant females in the Hawalli Province in Kuwait found 0.3% HBsAg positivity [35].

In 2006, the prevalence of HBsAg among pregnant was 7.1% in Oman, 1% Qatar [36].

In Saudi Arabia, HBsAg prevalence in pregnant females ranged from 2.44% in 2005 to 4.1% in 2012 [37–39]. In a recent meta-analysis in 2018, the pooled prevalence of HBsAg in Saudi Arabia was 2.63% (95% CI 2.17–3.18%) [27].

In a recent study in Turkey on 11,015 refugee Syrian pregnant patients, HBsAg prevalence was found to be 1.1% between 2012 and 2018 [40].

Table 2 WHO targets indicators in the different countries in Asia–Pacific

	HepB3 coverage*	HepB-BD coverage*	Prevalence national	HBsAg prevalence for children < 5 years	HBsAg prevalence for pregnant females (recent data)
North Asia					
Russia	97% in 2019 [6]	NA	0.6% in 2019 (modeled) [5] [https://www.globalhep.org/country-data-dashboards]	0.03% in 2019 (modeled) [5] [https://www.globalhep.org/country-data-dashboards]	0.7% in 2014 [7]; 0.5% in 2015 [7]
Central Asia					
Afghanistan	66% in 2019 [6]	37% in 2019 [6]	5.9% in 2019 (modeled) [5]	1.66% in 2019 (modeled) [5]	1.14% in 2010 [11]
Kazakhstan	97% in 2019 [6]	93% in 2019 [6]	2.26% in 2019 (modeled) [5]	0.22% in 2019 (modeled) [5]	1.2% in 2016 [12]
Kyrgyzstan	95% in 2019 [6]	96% in 2019 [6]	2.55% in 2019 (modeled) [5]	0.64% in 2019 (modeled) [5]	NA
Tajikistan	97% in 2019 [6]	99% in 2019 [6]	2.52% in 2019 (modeled) [5]	0.29% in 2019 (modeled) [5]	10.1% in 2015 [13]
Turkmenistan	99% in 2019 [6]	99% in 2019 [6]	2.65% in 2019 (modeled) [5]	0.38% in 2019 (modeled) [5]	NA
Uzbekistan	96% in 2019 [6]	99% in 2019 [6]	4.34% in 2019 (modeled) [5]	0.42% in 2019 (modeled) [5]	NA
Western Asia					
Armenia	92% in 2019 [6]	96% in 2019 [6]	2.09% in 2019 (modeled) [5]	0.16% in 2019 (modeled) [5]	0.2% in 1998, 0.5% in 1999 [14]
Azerbaijan	94% in 2019 [6]	98% in 2019 [6]	3.22% in 2019 (modeled) [5]	0.56% in 2019 (modeled) [5]	1.5% in 2010 [15]
Bahrain	99% in 2019 [6]	98% in 2019 [6]	2.64% in 2019 (modeled) [5]	0.12% in 2019 (modeled) [5]	NA
Cyprus	94% in 2019 [6]	NA	0.7% in 2019 (modeled) [5]	0.02% in 2019 (modeled) [5]	NA
Georgia	94% in 2019 [6]	94% in 2019 [6]	1.48% in 2019 (modeled) [5]	0.24% in 2019 (modeled) [5]	NA
Iran	99% in 2019 [6]	95% in 2019 [6]	1.53% in 2019 (modeled) [5]	0.09% in 2019 (modeled) [5]	1.3% in 2004 [17], 0.7% in 2011[18], 1.2% in 2012 [19], 0.8% in 2014 [20], 1.2% in 2014 [21], 0.4% in 2014 [22], 1.6% in 2015 [23], 0.59% in 2015 [24], 1.56% in 2015 [25], 0.18% in 2016 [26]
Iraq	84% in 2019 [6]	41% in 2019 [6]	1.98% in 2019 (modeled) [5]	0.43% in 2019 (modeled) [5]	5% in 2011 [28], 0.13% in 2017 [29]
Israel	96% in 2019 [6]	95% in 2019 [6]	0.53% in 2019 (modeled) [5]	0.04% in 2019 (modeled) [5]	0.3% in 2007 [31], 0.2% in 2014 [32]
Jordan	89% in 2019 [6]	NA	3.37% in 2019 (modeled) [5]	0.53% in 2019 (modeled) [5]	4.3% in 2002 [33], 5% in 2020 [34]
Kuwait	91% in 2019 [6]	93% in 2019 [6]	1.17% in 2019 (modeled) [5]	0.07% in 2019 (modeled) [5]	0.3% in 2012–2013 [35]
Oman	99% in 2019 [6]	99% in 2019 [6]	2.5% in 2019 (modeled) [5]	0.09% in 2019 (modeled) [5]	7.1% in 2006 [36]
Qatar	98% in 2019 [6]	97% in 2019 [6]	1.4% in 2019 (modeled) [5]	0.1% in 2019 (modeled) [5]	1% in 2006 [36]
Saudi Arabia	97% in 2019 [6]	96% in 2019 [6]	2.72% in 2019 (modeled) [5]	0.15% in 2019 (modeled) [5]	2.44 in 2005 [37], 1.6% in 2008 [38], 4.1% in 2012 [39]
Syria	54% in 2019 [6]	NA	3.08% in 2019 (modeled) [5]	0.82% in 2019 (modeled) [5]	1.1% in 2018 [40]
Turkey	99% in 2019 [6]	99% in 2019 [6]	2.43% in 2019 (modeled) [5]	0.17% in 2019 (modeled) [5]	1.6% in 2010 [41], 1.47% in 2011 [42], 3.3% in 2011[43], 2.9% in 2011 [44], 5.7% in 2013 [45], 4% in 2015 [46], 1.2% in 2014 [47], 0.9% in 2016 [48], 1.5% in 2016 [49], 1.8% in 2018 [40]
United Arab Emirates	98 in 2019 [6]	91% in 2019 [6]	1.82% in 2019 (modeled) [5]	0.12% in 2019 (modeled) [5]	1.5% in 2006 [36]
Yemen	73% in 2019 [6]	NA	5.46% in 2019 (modeled) [5]	1.63% in 2019 (modeled) [5]	10.8% in 2011 [50]

Table 2 (continued)

	HepB3 coverage*	HepB-BD coverage*	Prevalence national	HBsAg prevalence for children < 5 years	HBsAg prevalence for pregnant females (recent data)
East Asia					
China Mainland	99% in 2019 [6]	97% in 2019 [6]	5% in 2019 [51]	0.30% in 2019 (modeled) [5]	3.4% in 2010 in Haimen City [57], 5.49% in 2011 in Shenyang [58], 6.7% in 2012 (10 centers) [59], 3.2% in 2014 in 4 provinces [60], 7.07% in 2015 in Shaanxi province [61], 3.1% 2016 in Shenyang [62]
Mongolia	98% in 2019 [6]	98% in 2019 [6]	4.28% in 2019 (modeled) [5]	0.29% in 2019 (modeled) [5]	NA
South Korea (Republic of Korea)	98% in 2019 [6]	92% in 2019 [6]	2.95% in 2019 (modeled) [5]	0.10% in 2014 [64]	3.32% in 2012 [67]
North Korea (Democratic People's Republic of Korea)	97% in 2019 [6]	98% in 2019 [6]	10.47% in 2019 (modeled) [5]	0.61% in 2019 (modeled) [5]	NA
Japan	99% in 2019 [6]	99% in 2019 [6]	3.04% in 2019 (modeled) [5]	0.20% in 2019 (modeled) [5]	0.5% in 2011 [68]
Taiwan	97.8% in 2016 [70]	NA	7.85% in 2019 (modeled) [5]	0.16% in 2019 (modeled) [5]	5.9% in 2016 [71]
South-East Asia					
Brunei	99% in 2019 [6]	NA	2.11% in 2019 (modeled) [5]	0.1% in 2011 [64]	3.2% in 1990 [74], 1.02% in 2011 [75]
Cambodia	92% in 2019 [6]	88% in 2019 [6]	6.55% in 2019 (modeled) [5]	0.56% in 2017 [72]	4.39% in 2017 [72]
Indonesia	85% in 2019 [6]	84% in 2019 [6]	3.62 in 2019 (modeled) [5]	0.62 in 2019 (modeled) [5]	2.2% in 2014 in Jakarta [76], 2.76% in 2015 in 12 provinces [77], 6.1% in 2019 in Bandung [78]
Lao PDR	68% in 2019 [6]	55% in 2019 [6]	8.66% in 2019(modeled) [5]	1.7% in 2012 [64]	4.4% in 2011 [79], 2.9% in 2012 [80], 8.2% in 2013 [81], 5.44% in 2008–14 [82]
Malaysia	97% in 2019 [6]	99% in 2019 [6]	1.26% in 2019 (modeled) [5]	0.09% in 2019 (modeled) [5]	1.35% in 2008 [83]
Myanmar	90% in 2019 [6]	17% in 2019 [6]	2.39% in 2019 (modeled) [5]	0.61% in 2019 (modeled) [5]	6.2% in 2016 [84]
Philippines	65% in 2019 [6]	50% in 2019 [6]	8.24% in 2019 (modeled) [5]	0.8% in 2018 [73]	9.6% in 2014 [85], 1.43% in 2018 [86]
Singapore	96% in 2019 [6]	91%.in 2019 [6]	2.69% in 2019 (modeled) [5]	0.3% in 2010 [64]	NA
Thailand	97% in 2019 [6]	99% in 2019 [6]	4.75% in 2019 (modeled) [5]	0.36% in 2019 (modeled) [5]	6.2% in 2016 at Thai-Myanmar border [84], 1.4% in 2018 [87]
Timor-Leste	83% in 2019 [6]	70% in 2019 [6]	4.13% in 2019 (modeled) [5]	1.35% in 2019 (modeled) [5]	2.8% in 2014 [88]
Vietnam	89% in 2019 [6]	79% in 2019 [6]	6.6% in 2019 (modeled) [5]	2.2% in 2012 [64]	12.6% in 2009 – 2012 in Khan Hoa Province [89], 9.45% in 2012 in 5 regions [90], 7.8% in 2012 – 2014 in Thai Nguyen province [91]
South Asia					
Bangladesh	98% in 2019 [6]	NA	2.16% in 2019 (modeled) [5]	0.13% in 2019 (modeled) [5]	0.4% in 2011 in rural areas [94]
Bhutan	97% in 2019 [6]	86% in 2019 [6]	2.62% in 2019 (modeled) [5]	0.16% in 2019 (modeled) [5]	NA

Table 2 (continued)

	HepB3 coverage*	HepB-BD coverage*	Prevalence national	HBsAg prevalence for children < 5 years	HBsAg prevalence for pregnant females (recent data)
India	91% in 2019 [6]	56% in 2019 [6]	2.93% in 2019 (modeled) [5]	0.52% in 2019 (modeled) [5]	0.25% in 2006 in South India [97], 1.1% in 2008 in North India [98]
Maldives	99% in 2019 [6]	99% in 2019 [6]	2.86% in 2019 (modeled) [5]	0.48% in 2019 (modeled) [5]	NA
Nepal	93% in 2019 [6]	NA	1.12% in 2019 (modeled) [5]	0.15% in 2019 (modeled) [5]	0.32% in 2019 [100]
Pakistan	75% in 2019 [6]	NA	2.3% in 2019 (modeled) [5]	0.54% in 2019 (modeled) [5]	> 12% in Bahawalpur, Hyderabad and Rahim Yar Khan regions in 2006–2007 [103–105], 0.34% in 2006 in Karachi [106], 1.37% in Swat in 2008 [107], 1.16% (0.96—1.37) in Peshawar district of Pakistan (in 2013–2014) [108], 2.78% in Rawalpindi in 2016–2017 [109]
Sri Lanka	99% in 2019 [6]	NA	1.5% in 2019 (modeled) [5]	0.07% in 2019 (modeled) [5]	NA
Pacific countries					
Australia	95% in 2019 [6]	NA	2.14 in 2019 (modeled) [5]	0.07 in 2019 (modeled) [5]	0.8% in South Wales in 2000 [114], 2% in 2 teaching hospitals in Sydney in 2003–2006 [115], 0.5% in Victoria between 2009 and 2017 [116]
New Zealand	92% in 2019 [6]	NA	0.9% in 2019 (modeled) [5]	0.07 in 2019 (modeled) [5]	Decreasing trends from 1997 to 2009 [118]
American Samao	NA	NA	5.38% in 2019 (modeled) [5]	0.2% in 2011[64]	NA
Cook Islands	98% in 2019 [6]	99% in 2019 [6]	3.27% in 2019 (modeled) [5]	0% in 2021 [64]	NA
Federated States of Micronesia	84% in 2019 [6]	70% in 2019 [6]	3.56% in 2019 (modeled) [5]	0.30% in 2016 [64]	NA
Fiji	99% in 2019 [6]	99% in 2019 [6]	3.63% in 2019 (modeled) [5]	0.47% in 2019 (modeled) [5]	6.6% in 1998 [123], 2% in 2011 [124]
French Polynesia	NA	NA	NA	0% in 2014 [64]	NA
Guam	NA	NA	5.03% in 2019 (modeled) [5]	0% in 2015 [64]	2% in 2014 [125]
Kiribati	94% in 2019 [6]	99% in 2019 [6]	7.47% in 2019 (modeled) [5]	3.3% in 2014 [64]	15.1% in 1998 [123], 9.2% in 2002–2003 [126]
Marshall Islands	82% in 2019 [6]	98% in 2019 [6]	4.17% in 2019 (modeled) [5]	1.2% in 2016 [64]	8% in 2003–2003 and 10% in 2007 [127]
Nauru	96% in 2019 [6]	88% in 2019 [6]	4.76% in 2019 (modeled) [5]	0.53% in 2019 (modeled) [5]	NA
New Caledonia	96% in 2017 [6]	96% in 2017[6]	6.8% in 2000 [121]	1.3% in 8–11 year old in 2001 [122]	1.7–2.9 in 1996–1999 [128]
Niue	99% in 2019 [6]	99% in 2019 [6]	3.6% in 2019 (modeled) [5]	0% in 2015 [64]	NA
Papua New Guinea	35% in 2019 [6]	25% in 2019 [6]	6.2% in 2019 (modeled) [5]	2.3% in 2013 [64], 3.29% in 2014–2019 [120]	NA
Pitcairn	NA	NA	NA	NA	NA
Samoa	58% in 2019 [6]	65% in 2019 [6]	5.24% in 2019 (modeled) [5]	0.10% in 2014 [64]	NA
Solomon Islands	94% in 2019 [6]	66% in 2019 [6]	6.33% in 2019 (modeled) [5]	3.1% in 2016 [64]	13.7% in 2008 [129], 13.8% in 2015 [130]

Table 2 (continued)

	HepB3 coverage*	HepB-BD coverage*	Prevalence national	HBsAg prevalence for children < 5 years	HBsAg prevalence for pregnant females (recent data)
Tokelau Islands	NA	NA	6.37% in 2019 (modeled) [5]	2.97% in 2019 (modeled) [5]	NA
Tonga	99% in 2019 [6]	99% in 2019 [6]	3.95% in 2019 (modeled) [5]	0.41% in 2019 (modeled) [5]	18.6% in 1998 [123]
Tuvalu	92% in 2019 [6]	98% in 2019 [6]	5.76 in 2019 (modeled) [5]	1.48 in 2019 (modeled) [5]	NA
Vanuatu	90% in 2019 [6]	82% in 2019 [6]	5.16 in 2019 (modeled) [5]	1.45 in 2019 (modeled) [5]	12.3% in 1998 [123]
Wallis and Futuna Islands	NA	NA	NA	0.9% in 2012 [64]	NA

HBsAg Hepatitis B surface antigen, *HepB3* coverage of all doses of HBV vaccine, *HepB-BD* timely hepatitis B vaccine birth dose

In Turkey, HBsAg prevalence in pregnant females ranges from 1.6% in 2010 to 1.8% in 2018 [40–49] (Table 2). In a recent meta-analysis in 2018, the pooled prevalence of HBsAg in Turkey was 2.84% (95% CI 2.68–3.01%) [27].

In 2011, the prevalence of HBsAg among pregnant in Yemen was 10.8% [50].

East Asia (China Mainland, Mongolia, North Korea, South Korea, Japan, and Taiwan)

The HBsAg national prevalence and children under 5-year-old prevalence were estimated to be 5% (in 2018) [51], and 0.30% (0.20–0.50%) (in 2019) in China Mainland, respectively [5]. In 2019, China Mainland achieved HepB3 coverage of 99%, and HepB-birth dose coverage of 97% [6]. In China Mainland, the prevalence of HBsAg in child-bearing-aged females has been extensively investigated in several large cross-sectional studies including several millions of females as part of the Triple Elimination of MTCT of HIV, HBV, and Syphilis [51]. Currently, in this age group (20–49 years old), the overall prevalence of HBsAg is around 5.5% (4.9–11.8%) [52–56].

Specifically, the HBsAg prevalence in pregnant females (mostly aged 26–28 years, varying from 16 to 47 years) has also been widely reported as 4.5%(3.0–7.0%), with around 37% (26–67%) of them being also positive for HBeAg [57–62].

The modeled HBsAg national and children under 5-year-old prevalence in 2019 were estimated to be 4.28% (95% CI 3.88–4.7%) and 0.29% (0.20–0.36%) in Mongolia, respectively [5]. In 2019, Mongolia achieved HepB3 coverage of 98%, and HepB-birth dose coverage of 98% [6]. In Mongolia, the prevalence of HBsAg is 9.4% in child-bearing-aged females [63].

The modeled HBsAg national prevalence and children under 5-year-old prevalence were estimated to be 2.95% (95% CI 2.81–3.1%) in 2019 [5], and 0.10% in 2014 [64] in South Korea (Republic of Korea), respectively. In 2019, South Korea (Republic of Korea) achieved HepB3 coverage of 98%, and HepB-birth dose coverage of 92% [6]. In South Korea (Republic of Korea), the prevalence of HBsAg in child-bearing-aged females (20–49 years) is 1.7–3.7% in recent years [65, 66]. In pregnant females, the HBsAg prevalence is 3.32% in 2012 [67].

The modeled HBsAg national and children under-5-year-old prevalence in 2019 were estimated to be 10.47% (95% CI 9.11–12.29%) and 0.61% (0.47–0.78%) in North Korea (Democratic People's Republic of Korea) [5]. In 2019, North Korea (Democratic People's Republic of Korea) achieved HepB3 coverage of 97%, and HepB-birth dose coverage of 98% [6]. There are no recent data on HBsAg prevalence in pregnant females in North Korea.

In 2019, the modeled HBsAg national prevalence and children under 5-year-old prevalence were estimated to be 3.04% (95% CI 2.67–3.37%) [5] and 0.20% (0.0–0.40%) in Japan, respectively [64]. In Japan, mother-to-child transmission is the major route of establishing chronicity of HBV, but it is less common than in other Asian countries. In 2019, Japan achieved HepB3 coverage of 99%, and HepB-birth dose coverage of 99% [6]. From June, 1985, all pregnant females were screened for the presence of serum HBsAg, and from January, 1986, the Government started financing programs for prevention of vertical transmission of HBV infection. This program involves HBsAg testing of all pregnant female and inoculation of anti-HBsAg human immunoglobulin (HBIG) and HBV vaccines to all infants born to HBsAg-positive mothers, which has led to extremely low prevalence of HBsAg in general population as well as pregnant female in Japan. In a recent study on pregnant female who gave birth at all delivery hospitals/clinics in Hiroshima prefecture between April 2010 and March 2011, it was found that overall HBsAg-positive rate was 0.51% (95% CI 0.40–0.63%), and an extremely low prevalence (0.10%; 95% CI 0.00–0.25%) was observed among pregnant female born after 1986. Perinatal HBV transmission is estimated to be almost completely inhibited in the next generation [68].

Taiwan is a success story of tackling hepatitis B virus infection. The modeled HBsAg national and children under-5-year-old prevalence in 2019 were estimated to be 7.85% (95% CI 7.5–9.19%) and 0.16% (0.13–0.18%) in Taiwan, respectively [5]. From epidemiology studies in Taiwan, the rate of HBsAg carriage was high in the general population (15–20%) before 1970; and more than 70% of hepatocellular carcinoma (HCC) was associated with chronic HBV infection [69]. To tackle this serious health problem, the Taiwan government launched a mass vaccination program against hepatitis B in July 1984, and the program was very successful in the prevention of new HBV infection in the young generations [69]. Statistics from the Ministry of Health and Welfare, Taiwan, revealed that the 2016 newborn HBV vaccination rate was as high as 97.8% [70]. To investigate the evolution of HBV infection status in pregnant mothers, Su et al. conducted a 32-year cross-sectional study using the data from the National Immunization Information System in Taiwan [71]. Maternal HBsAg and HBeAg data was collected from a screening program. The authors then used an age-period-cohort model to analyze 940 180 pregnant females collected in years 1996, 2001, 2006, 2011, and 2016, respectively. They found that the annual rate of HBsAg seropositivity decreased from 13.4% during 1984–1985 (before the era of nationwide vaccination) to 5.9% in 2016 (3 decades after vaccination program). The annual rate of HBeAg seropositivity decreased from 6.4% during 1984–1985 to 1.0% in 2016. Pregnant females born after July 1986 (the HBV vaccination cohort) had the lowest risk (relative risk = 0.27) of HBsAg positivity compared with those born before June 1984. After controlling the birth cohort effect, the rate of HBsAg carriage in pregnant female has been significantly decreased through the universal infant HBV immunization program. These findings suggested that the majority of perinatal HBV infection on the next generation will be prevented in Taiwan [71]. To further lower the risk of vertical transmission, new strategies in combination with the vaccination program have already been implemented in the post-immunization era in Taiwan, including the administration of birth dose HBIG and HBV vaccine to all newborns of chronic HBV-infected mothers and the administration of oral nucleos(t)ide analogue during the third trimester of pregnant females with high serum viral load.

Southeast Asia (Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, and Vietnam)

The HBsAg national prevalence and children under-5-year-old prevalence were 2.11% (95% CI 1.82–2.41%) in 2019 (modeled) [5] and 0.10% in 2011[64] in Brunei Darussalam, 6.55% (5.5–7.56%) in 2019 (modeled) and 0.56% in 2017 [72] in Cambodia, 3.62% (3.17–4.05%) in 2019 (modeled) and 0.62% (0.49–0.76%) [5] in Indonesia, 8.66% (7.32–10%) in 2019 (modeled) [5] and 1.7% (0.8–2.6%) in 2012 [64] in Lao PDR, 1.26%(1.14–1.38%) and 0.09% (0.07–0.12%) in 2019 (modeled) [5] in Malaysia, 2.39% (1.99–2.71%) and 0.61% (0.46–0.82%) in 2019 (modeled) [5] in Myanmar, 8.24% (7.2–9.36%) in 2019 (modeled) [5] and 0.70% in 2018 [73] in Philippines, 2.69% (2.52–2.86%) in 2019 (modeled) [5] and 0.30% in 2010 [64] in Singapore, 4.75% (4.43–5.09%) and 0.36% (0.28–0.45%) in 2019 (modeled) [5] in Thailand, 4.13% (3.34–4.93%) and 1.35% (1.01–1.80%) in 2019 (modeled) [5] in Leste, and 6.6% (6.3–6.92%) in 2019 (modeled) [5] and 2.20% (1.5–3.10%) in 2011 [64] in Vietnam, respectively (Table 2).

In 2019, HepB3/HepB-birth dose coverage was 92%/88% in Cambodia, 85%/84% in Indonesia, 68%/55% in Lao PDR, 97%/99% in Malaysia, 90%/17% in Myanmar, 65%/50% in Philippines, 96%/91% in Singapore, 97%/ 99% in Thailand, 83%/70% in Timor-Leste, and 89%/79% Vietnam, respectively [6]. In 2019, HepB3 coverage was 99% in Brunei Darussalam [6].

As reported in Table 2, HBsAg prevalence among pregnant females is > 2% for all the countries in Southeast Asia (intermediate level) with data available and > 7–8% for some of them (high level). However, many of these data were reported 10 years ago and recent national seroprevalence surveys are missing.

One old study in 1990 found 3.2% HBsAg positivity in pregnant females of Brunei Darussalam [74]. Another study done in a tertiary care hospital (in 2011) in Brunei found

HBsAg positivity to be 1.02%, significantly higher among the Chinese (2.4%), indigenous (4.0%), and expatriates (1.5%) than among the Malays (0.8%) [75].

One survey conducted among children (5–7 years old) born during 2010–2012 and their mothers in Cambodia found overall HBsAg positivity of 4.39% (95% CI 3.53–5.45%) among mothers and 0.56% (95% CI 0.32–0.98%) among children. HBsAg positivity was higher among children without hepatitis B vaccination [4.62% (95%CI 1.31–14.97%)], and among children with an HBsAg-positive mother [10.11% (95%CI 5.41–18.11%)]. Although hepatitis B vaccination birth dose (HepB-BD) was received by 78.4% of the children, only 54.4% received the birth dose timely [72].

In Indonesia, HBsAg prevalence of 2.2% was found among pregnant females in Jakarta (in 2014) [76]. HBsAg prevalence among 69,891 pregnant females across 12 provinces in Indonesia was 2.76% in 2015, with the lowest found in West Sumatra Province (1.6%) and the highest in West Papua Province (8.0%) [77]. A study conducted from July 2018 to April 2019 in 27 midwifery clinics and one private obstetric clinic in Bandung (Indonesia) found HBsAg positivity of 6.1% among the pregnant females [78].

In Loa PDR, in studies on children and mother pairs, HBsAg prevalence was found to be 4.4% (95% CI 3.0–5.7%) in 2011 [79] and 2.9% (95% CI 1.7–4.2%) in mothers in 2012 [80]. Another study has found HBsAg prevalence of 8.2% in 2013 [81]. In a recent retrospective study from Lao PDR, performed in a Hospital Laboratory on pregnant females from 2008 to 2014, showed overall HBsAg positivity of 5.44% (95 CI 5.1–5.8%), with the annual prevalence ranging from 4.6 to 6.2%. A slight but steady and significant decrease in prevalence over the 7 years of the study could be documented [82].

In a cross-sectional study of antenatal mothers who attended government health clinics in Ipoh (Malaysia) between July 2008 and October 2008 found HBsAg prevalence of 1.35% [83].

Among females tested (2012–2016) in antenatal clinics on the Thai-Myanmar border (immigrants and refugees from Myanmar), overall confirmed HBsAg prevalence was 6.2% [84].

In a study among pregnant subjects attending prenatal clinic at the Philippine General Hospital from January to July 2014, HBsAg positivity was found to be 9.6% [85], whereas another study found HBsAg prevalence of 1.43% in pregnant females admitted to a tertiary hospital in Philippines (from 2014 to 2018) [86].

In a recent hospital-based study from Thailand, on pregnant females attending antenatal clinics (2015–2018), HBsAg prevalence was 1.4% [87].

In a study on females delivering at private clinic (2013–2014) in Timor-Leste HBsAg prevalence was 2.8% [88].

In studies from Vietnam, HBsAg prevalence was 12.6% (95% CI 11.1–14.0%) in Khan Hoa Province, central Vietnam in 2009–2012 [89], 9.45% in 2012 in 5 regions [90], and 7.8% in 2012–2014 in Thai Nguyen province [91].

In these countries with high-prevalence populations, infant vaccination against HBV is crucial. Most of the countries in South-East Asia have achieved > 90% HepB3 coverage (excepting a few countries like Indonesia, Lao PDR, Philippines, Timor-Leste, and Vietnam) and > 50% of HepB-birth dose coverage (except Myanmar) as recommended by WHO for 2020. Currently > 90% HepB-birth dose coverage has been achieved by some of the countries (Malaysia, Singapore, and Thailand) (Table 2). However, as reported in Table 2, HBsAg prevalence for children 5 years old remains > 1% in a few countries (Lao PDR, Timor-Leste, and Vietnam) (WHO 2020 target) and > 0.1% in most of the countries (WHO 2030 target).

South Asia (Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka)

In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.16% (95% CI 1.97–2.35%) and 0.13% (0.10–0.16%) in Bangladesh, respectively [5]. In 2019, HepB3 dose coverage was 98% in Bangladesh [6]. In one old study (1992), HBsAg was positive in 3.6% in 500 pregnant mothers [92]. In another study on 1800 pregnant females who delivered from October 1995 to January 1996 at Dhaka Medical College Hospital, 63 of 1800 or 3.5% of the mothers were found to be HBsAg positive. Of the 63 HBsAg-positive mothers, 19 (30.2%) were found to be HBeAg positive. Only two of the HBsAg-positive mothers had established acute infection [93]. More recent studies have found decreasing trend. In a study (2011), HBsAg was positive in 0.4% of pregnant females in rural Bangladesh. This study was done years after incorporating hepatitis B vaccination schedule in the Expanded Program on Immunization (EPI) to vaccinate the children in rural Bangladesh; the prevalence is gradually declining [94].

In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.62% (95% CI 2.53–2.73%) and 0.16% (0.13–0.17%) in Bhutan, respectively [5]. In 2019, HepB3/HepB-birth dose coverage was 97%/86% in Bhutan [6]. Data on HBsAg prevalence in pregnant females are lacking from Bhutan.

In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.93% (95% CI 2.57–3.29%) and 0.52% (0.42–0.63%) in India, respectively [5]. In 2019, HepB3/HepB-birth dose coverage was 91%/56% in India [6]. Many studies from the Indian subcontinent have

looked specifically at the prevalence of HBsAg positivity in pregnant females. However, only very few studies were sufficiently large, with adequate number of females screened, to reach a meaningful conclusion. In one old study, HBsAg positivity in pregnant female was 3.7% in 1987[95] and 1% in 1999 in North India [96]. More recent studies have found lower HBsAg prevalence in pregnant females: 0.25% in 2006 in South India [97] and 1.1% (2004–2008) in North India [98]. In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.86% (95% CI 2.37–3.39%) and 0.48% (0.34–0.64%) in Maldives, respectively [5]. In 2019, HepB3/HepB-birth dose coverage was 99%/99% in Maldives, respectively [6].

Nepal belongs to low endemic zone according to Hepatitis B surface antigen (HBsAg) seroprevalence, as the overall prevalence of hepatitis B in Nepal is estimated at 0.9% [99]. In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 1.12% (95% CI 1.02–1.23%) and 0.15% (0.11–0.18%) in Nepal, respectively [5]. In 2019, HepB3 coverage was 93% in Nepal [6]. In a nested prospective case study (2019), Shedain et al. found prevalence values of HBV 0.32% in 16,400 of pregnant females who attended a tertiary-level hospital over a period of 1 year. The infection was clustered in the indigenous ethnicities, nearly threefold higher infection compared to other than indigenous ethnicities. According to some authors, increased alcohol consuming pattern; seen in those indigenous communities, which can lead to increase the sexual risk behavior and unsafe sexual relationship that may be responsible for this high prevalence in those communities [100].

The overall prevalence of HBsAg was 2.5% in a prevalence survey carried out in 2010 to obtain national estimates on hepatitis B and C infections in Pakistan [101]. In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.3% (95% CI 2.04–2.61%) and 0.54% (0.43–0.68%) in Pakistan, respectively [5]. In 2019, HepB3 coverage was 75% in Pakistan [6]. Most of the studies from Pakistan on the prevalence of hepatitis B in pregnancy are hospital-based. One meta-analysis (2011) of nine studies showed the HBV prevalence of 5.872% ± 4.984% in pregnant females in Pakistan [102]. This extensive heterogeneity is due to the difference in the prevalence of hepatitis B in different regions of Pakistan and different periods. A very high frequency of ≥ 12% HBV infection in pregnant females has been reported in Bahawalpur, Hyderabad, and Rahim Yar Khan regions in 2006–2007 [103–105]. Other studies have found lower prevalence. Among pregnant females prevalence of HBsAg was found to be 0.34% in 2006 in Karachi [106], 1.37% in Swat in 2008 [107], 1.16% (95% CI 0.96–1.37%) in Peshawar district of Pakistan (in 2013–2014) [108], and 2.78% in Rawalpindi in 2016–2017 [109]. Moreover, HBsAg was generally reported with low frequency in private-sector patients and high in public-sector patients.

In Sri Lanka, the prevalence of HBsAg is generally low. In 2019, the modeled HBsAg national prevalence and under-5-year-old prevalence were 1.5% (95% CI 1.34–1.66%) and 0.07% (0.06–0.10%) in Sri Lanka, respectively [5]. In 2019, HepB3 coverage was 99% in Sri Lanka [6]. In Sri Lanka, although no specific studies on prevalence of HBV infections among pregnant mothers are available, it is reasonable to presume the prevalence is likely to be much lower than in the neighboring countries.

Pacific Countries (Australia, New Zealand, and Pacific Island Countries and Territories)

Australia, New Zealand (NZ), and Pacific Island Countries and Territories (PICT) fall within the World Health Organization (WHO) Western Pacific Region which has a high prevalence of HBV and related morbidity [110]. The PICT consist of three regions incorporating many countries: Melanesia (comprising Fiji, New Caledonia, Papua New Guinea, the Solomon Islands, and Vanuatu); Micronesia (comprising the Federal States of Micronesia, Guam, Kiribati, Marshall Islands, Nauru, Palau); and Polynesia (comprising Samoa, American Samoa, Tonga, Cook Islands, Tuvalu, Tokelau, Niue, Wallis and Futuna, French Polynesia and the Pitcairn Islands).

New Zealand and Australia introduced universal HBV vaccination of infants in 1988 and 2000, respectively. By the year 2000, both NZ and Australia had introduced catch-up vaccination programs for adolescents and other high-risk groups [111]. In both the countries, birth dose HBV vaccination within 24 h of birth, along with hepatitis B immune globulin (HBIG), is given to infants born to HBsAg-positive mothers. Overall health outcomes are poorer and burden of communicable and noncommunicable diseases greater among indigenous peoples (Aboriginal and Torres Strait Islander people in Australia and Māori in New Zealand) as compared with non-Indigenous peoples. Immigration from other Asia–Pacific countries with high HBV prevalence is also common in Australia and NZ [110].

In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.14% (95% CI 1.94–2.34%) and 0.07% (0.06–0.09%) in Australia, respectively [5]. In 2019, HepB3 dose coverage was 95% in Australia [6]. In Australia, the majority of chronic HBV infections occur in migrants from endemic areas and their children, and also HBV prevalence is higher in Indigenous peoples (Aboriginal and Torres Strait Islander people) [112]. In Australia, 0.4–1.3% of pregnant females are chronically infected with HBV keeping with the low prevalence in general population [113]. HBsAg prevalence in pregnant females was 0.8% in South Wales in 2000 [114], 2% in 2 teaching hospitals in Sydney (2003–2006) [115], and 0.5% in Victoria among mothers of all singleton births between 2009 and 2017 [116].

In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 0.9% (95% CI 0.78–1.01%) and 0.07% (0.05–0.08%) in New Zealand, respectively [5]. In NZ, Māori, Pacific, and Asian New Zealanders have higher HBV prevalence than European New Zealanders [117]. In 2019, HepB3 dose coverage was 92% in New Zealand [6]. A clear downwards trend was found in antenatal hepatitis B prevalence rates from 1997 to 2009 in one study, and is likely to be as a result of the introduction of the hepatitis B vaccine onto the universal schedule throughout New Zealand in 1988 [118].

The Pacific Islands and Territories (PICT) are very diverse socio-culturally, economically, geographically, and demographically [119].

The majority of PICTs are low-income and middle-income countries. Pacific Island Countries and Territories have moderate–high HBsAg prevalence (Table 2). The HBsAg national prevalence and children under-5-year-old prevalence were 5.38% (95%CI 4.45–6.28%) in 2019 (modeled) [5] and 0.20% in 2011 [64] in American Samoa, 3.27% (2.69–3.74%) in 2019 (modeled) [5] and 0% in 2012 [64] in Cook Islands, 3.56% (3.11–4.03%) in 2019 (modeled) [5] and 0.30% (0.10–0.50%) in 2016 [64] in Federated States of Micronesia, 3.63% (3.15–4.1%) in 2019 (modeled) [5] and 0.47% (0.34–0.58%) in 2019 (modeled) [5] in Fiji, 5.03% (4.31–5.86%) in 2019 (modeled) [5] and 0% in 2015 [64] in Guam, 7.47% (6.13–8.88%) in 2019 (modeled) [5] and 3.30% (2.4–4.6%) in 2014 [64] in Kiribati, 4.17% (3.52–4.86%) in 2019 (modeled) [5] and 1.20% (0.60–1.90%) in 2016 [64] in Marshall Islands, 4.76% (3.87–5.7%) in 2019 (modeled) [5] and 0.53% (0.36–0.69%) in 2019 (modeled)[5] in Nauru, 3.61% (2.92–4.23%) in 2019 (modeled) [5] and 0% in 2015 [64] in Niue, 6.2% (5.82–6.47%) in 2019 (modeled) [5] and 3.29% in 2014–2019 [120] in Papua New Guinea, 5.24% (4.25–6.3%) (modeled in 2019) [5] and 0.10% in 2014 [64] in Samoa, 6.33% (4.87–7.42%) (modeled in 2019) [5] and 3.1%(2.0–4.9%) in 2016 [64] in Solomon Islands, 6.37% (5.21–7.67%) in 2019 (modeled) [5] and 2.97% (1.99–4.12%) in 2019 (modeled) [5] in Tokelau Islands, 3.95% (3.23–4.59%) in 2019 (modeled) [5] and 0.41% (0.24–0.55%) in 2019 (modeled) [5] in Tonga, 5.76% (4.79–6.68%) in 2019 (modeled) [5] and 1.48% (1.03–2.0%) in 2019, (modeled) [5] in Tuvalu, and 5.16% (4.21–6.18%) in 2019 (modeled) [5] and 1.45% (0.96–1.95%) in 2019 (modeled) [5] in Vanuatu respectively. One study found HBsAg prevalence of 6.6% in young military recruits in 2000 in New Caledonia [121]. HBsAg prevalence was 1.3% in children 8–11 years in 2001 in New Caledonia [122].

HBV vaccination for infants and children started between 1995 and 1997 in all PICT, including birth dose delivery in most countries. Younger age at first pregnancy in PICT increases risk of mother-to-child transmission, as a greater proportion of young mothers are HBV envelope antigen (HBeAg) positive with high viral load. In 2019, HepB3/HepB-birth dose coverage was 98%/99% in Cook Islands, 84%/70% in Federated States of Micronesia, 99%/99% in Fiji, 94%/99% in Kiribati, 82%/98% in Marshall Islands 96%/99% in Nauru, 99%/99% in Niue 35%/25% in Papua New Guinea, 58%/65% in Samoa, 94%/66% in Solomon Islands, 99%/99% in Tonga, 92%/98% in Tuvalu, and 90%/82% in Vanuatu, respectively.[6].

One of the largest and most complete HBsAg prevalence studies in PICT was by Wilson et al. who reported HBsAg prevalence based on serological surveys conducted in 1998 (across Fiji, Vanuatu, Tonga, and Kiribati as part of a vaccination efficacy study (published 2000, after HBV vaccination introduction). The survey found HBsAg prevalence among pregnant females of 6.6% in Fiji, 15.1% in Kiribati, 18.6% in Tonga, and 12.3% in Vanuatu [123].

HBsAg prevalence of 2% was found in antenatal females in 2011 in Nausori, Fiji [124].

HBsAg prevalence was 2% in 2014 in Guam among pregnant females [125].

A study conducted in 2002 and 2003 found HBsAg prevalence of 9.2% (CI 4–15%) in 269 pregnant females in Tarawa, Kiribati [126].

HBsAg prevalence in Marshallese pregnant females was 8% in 2003–2003 and 10% in 2007 [127].

Studies conducted in the East-Coast provincial hospital (New Caledonia) (from 1996 to 1999) found HBsAg prevalence ranging from 1.7 to 4.9% in pregnant females [128].

In Solomon Islands, among pregnant females, studies have found HBsAg prevalence of 13.7% in 2008 (antenatal cohort in Honiara, Gizo, and Munda) [129], and 13.8% in 2015 among pregnant females attending antenatal clinic in Honiara [130].

Areas of future research

Countries need to generate accurate and large-scale data on prevalence of HBsAg in pregnant females, and their virological characteristics.

Immunopathogenesis of hepatitis B virus infection (acute and chronic) in pregnancy

Review of literature

Immunopathogenesis of acute HBV infection in pregnancy

There is scarcity of reports on acute hepatitis B infection in pregnancy; however, it seems that the clinical course does not differ from pregnant females to non-pregnant females [131]. The usual disease course would likely be uneventful. Under a very rare circumstance, fulminating hepatitis occurs.

Natural history of HBV infection is determined by complex interactions between virus and the host immune response [132]. In pregnancy, maternal immunity is totally altered to tolerate semi-foreign body of fetus, and also pregnancy is associated with increased adrenal corticosteroids and other hormones that play a significant role in altering host immunity and viral replication.

There are greater chances of acute liver failure in pregnancy due to acute HBV infection, but at the same time, others have reported none of the detrimental effect of pregnancy on clinical recovery in acute HBV infection [133].

Due to weak T-cell response, HBsAg loss and seroconversion may be delayed in the pregnant females with acute hepatitis B than non-pregnant [131]. T cells are markedly reduced during early pregnancy up to the 20th week of gestation to reduce the level of immunity. Increased hormone levels during pregnancy, including progesterone, estrogen, and human chorionic gonadotropin, have been shown to have a clear suppressive effect on cell-mediated immunity. HBV-specific CD8 T cells play a pivotal role in clearing the acute HBV infection; however, it is observed that HBV-specific T-cell responses are weaker or absent in pregnant females than non-pregnant females or adult males [134].

Immunopathogenesis of chronic HBV infection in mothers during pregnancy and postpartum period

The immunological changes during pregnancy and the postpartum period affect the natural history of chronic HBV infection. Biochemical hepatic flares and higher rates of HBeAg loss (and HBsAg clearance) have been reported in the early postpartum period due to immune reconstitution [135]. Most flares are self-limited and do not require therapy, but some can be severe, resulting in liver failure [136]. HBeAg-positive mothers have higher incidence of ALT flares as compared to the HBeAg-negative mothers. HBeAg titers < 1:650 among HBeAg-positive mothers have been shown to be associated with HBeAg clearance in the postpartum period [137]. Immunological changes (like regulatory T-cell expansion and an increase in Th1 cytokines, IFN-γ, and IL-12) occurring during pregnancy to prevent fetus rejection are reversed after delivery [138].

There are also some differences in immune responses among HBeAg-positive mothers (higher frequency of CD19 + B cells, lower frequency of CD3 + CD4 + T cells, and peripheral NK-cell inhibition) as compared to HBeAg-negative mothers [139].

Reactivation of chronic HBV infection has also been reported during pregnancy [140]. Cortisol levels peak at around delivery, and a sudden decrease in levels during postpartum period has effects similar to steroid withdrawal, causing HBV reactivation. Defective HBV-specific T-cell responses also occur in the peripartum period [141].

Immunopathogenetic mechanisms involved in MTCT

HBV MTCT can potentially occur prenatal or intra-uterine, natal or at the time of birth, and postpartum. Most HBV infections occur perinatally (at birth or soon after) in unvaccinated infants, but historically reports have suggested that approximately 3% to 8% of infections may occur through the intra-uterine route [142]. However, the findings that, after administration of HBIG and hepatitis B vaccine in newborn infants, MTCT of HBV occurs only in 2–3% of infants born to HBsAg-positive mothers (< 0.1% of infants of HBeAg-negative mothers and 5–10% of infants of HBeAg-positive mothers) clearly indicate that historically estimated intra-uterine transmission appears to be overstated. It is believed that intra-uterine transmission of HBV is the most significant contributor to MTCT and immunoprophylaxis failure [see below].

The presence of HBeAg and other viral proteins (like HBx) can affect the risk of MTCT. Maternal HBeAg seropositivity is a significant risk factor for MTCT. In chronic HBV infection, HBeAg has an immunomodulatory role, and early in utero exposure to HBeAg may promote chronicity instead of viral clearance [143].

Studies in mouse models have shown that conditioning of hepatic macrophages by maternal HBeAg generates anti-inflammatory macrophages, which lead to HBV persistence. However, in the absence of HBeAg preconditioning, macrophages acquire a proinflammatory phenotype, leading to HBV clearance by activated CD8 + T cells [144].

In pregnant females with viral loads of > 3 log10 copies/mL, functional hepatitis B X protein (HBx) produced in HBV-infected placenta cells could activate phosphoinositide 3-kinase in placenta, which signals inhibition of apoptosis in placental cells, allowing for HBV persistence in trophoblasts [145].

High viral load is a known significant risk factor for MTCT [see below]. Placental infection occurs progressively through different cellular layers from maternal to the fetal side, with the depth of placental tissue infection in direct proportion to maternal viral load [146].

Occult HBV infection (OBI) is characterized by serum HBsAg negativity with or without serum antibodies (anti-core and/or anti-HBs), and HBV DNA in serum or liver or extra-hepatic reservoirs (peripheral blood mononuclear cells or lymphoid system). OBI may occur in infants born to HBsAg-positive mothers despite the receipt of immunoprophylaxis. Most studies show very low or no OBI in vaccinated children born to HBsAg-positive mothers [147]. Further studies are needed to assess the vertical transmission of OBI and its clinical implications.

In one Japanese study, genotype C was associated with increased perinatal transmission rates as compared to genotype B. However, the increased MTCT risk may be due to higher viral loads and HBeAg positivity in mothers with HBV genotype C infection [148]. Other studies did not find an association between MTCT risk and the HBV genotype [149].

Naturally occurring HBV variants are selected under host pressure. One study found that in HBeAg-negative pregnant females having precore mutant G1896A and HBV DNA levels of 4–5 log10 copies/mL, HBV transplacental transmission did not occur (no HBV DNA was found in the analyzed placenta), and no passive-active immunoprophylaxis failure was seen in the infants at 1 year of age [150]. Another retrospective study from China Mainland suggested that dual basal core promoter mutants have a protective role in MTCT, as these were found in mothers who did not transmit HBV to their neonates; but this association may also be related to lower maternal viral loads in pregnant females with dual basal core promoter mutants [151].

Impaired dendritic cell function and decreased levels of follicular T cells (CD4 + C-X-C chemokine receptor type 5 +), plasma B cells (CD19 + CD38 +) within PBMCs, and low serum IL-21 were found in mothers in association with MTCT, versus mothers who did not transmit HBV to their infants. Also, newborns showed transcriptomic imprints of their mothers, suggesting that mothers' immune signatures could be a potential marker for MTCT [152, 153].

Hepatitis B vaccine-specific responses in infants born to mothers who were HBsAg positive and role in immune response to HBV vaccine

One Taiwanese study found that only 16% of the peoples who had received the HBV vaccine as infants had anti-HBs at 15 years of age [154]. The factors associated with blunted immune response in infants born to HBsAg-positive and HBeAg-positive mothers include transplacental passage of HBsAg and transient HBsAg positivity in the infants [155].

Increasing the vaccine dose from 10 to 20 μg improved the immunogenicity among the infants born to HBeAg-positive mothers [156]. Also, HBV vaccine alone is as effective as the combination of HBIG plus vaccine, in preventing HBV infection in infants born to HBeAg-negative mothers [157].

Lower amounts of the T helper 1 cytokine IL-2 secretion in an in vitro stimulation assay has been found to be associated with vaccine failure among infants receiving the complete immunoprophylaxis [158]. I*n utero* encounter to HBV antigens is suggested by the HBV-specific T-cell responses in uninfected vaccinated infants born to HBeAg-negative chronic HBV-infected mothers; although this exposure does not impair the neonatal B-cell and T-cell responses to the HBV vaccine [159]. HBV-specific T-cell responses can be seen in children for up to 10 years after their primary infant vaccination, despite having negative or low anti-HBs levels [160].

Trained immunity in infants born to mothers who were HBsAg positive and role in immunoprophylaxis failure

Exhaustion of HBV-specific CD8 + T-cell responses is one of the mechanisms for HBV persistence. Diminished expression of CD3 + T-cell receptor zeta chain is associated with functionally defective CD8 + T cells (producing less interferon-γ) and reduced expression of the cytotoxicity marker CD107a in HBsAg-positive newborns versus HBsAg-negative and healthy newborns [161]. HBsAg-positive pregnant females have also shown immature transitional B cells and decreased plasma B cells continuously from third trimester till delivery. Also, higher pre-vaccination levels of immature transitional B cells were found in HBsAg-positive newborns compared with HBsAg-negative infants born to HBsAg-positive mothers. The frequency of immature transitional B cells declined at 12 months after vaccination in HBsAg-positive newborns, whereas no changes were observed in HBsAg-negative and uninfected healthy newborns [162]. Although, these novel observations added a new perspective in understanding the key mechanisms of HBV chronicity in newborns, yet it is unknown when this phenomenon starts during pregnancy; therefore, it may be worthwhile to analyze the kinetics of TCR zeta expression and regulatory T cells throughout pregnancy.

Serum cytokine profiling from neonates born to HBsAg-positive mothers revealed a cytokine signature compatible with a Th1-like response (high levels of IL-12 p40 and low levels of Th2 cytokines IL-4, IL-5, IL-13, and IL-10) and a decrease in proinflammatory cytokine profile (IL-1β and IL-6). Also, cord blood mononuclear cells from neonates who were HBsAg positive showed a stronger response compared to healthy controls to an unrelated bacterial challenge. Despite increased levels of IL-12p40 and IFN-α2 in HBV-induced trained immunity, HBV-specific T-cell response was lacking which indicates that trained immunity may induce monocytes in cord blood to fight against other pathogens, but does not help in HBV clearance [163]. It is presumed that placental DCs and neutrophils secrete IL-12p40, and thus play a direct role in the modulation of maternal or neonatal infections. Maternal HBeAg "trains" Kupffer cells in utero, thus playing a role in HBV persistence [144].

Areas of future research

Further studies are necessary in serially collected samples from mothers and infants to clearly understand the dynamics

of the host immune response in association with HBV flares and MTCT.

Although combined maternal HBeAg positivity and high viral loads is an established risk factor for MTCT, HBV genotype, PC/BCP mutations, and risk of immunoprophylaxis failure is not well understood and may be an area of future studies.

Further studies are needed to assess the vertical transmission of OBI despite appropriate immunoprophylaxis and its clinical implications.

How hepatitis B virus infection (acute and chronic) impacts the health of pregnant females and outcome of pregnancy

Review of literature

Many epidemiologic studies have reported possible impact of maternal HBV infection on the perinatal and pregnancy-related outcomes. However, results from studies have been contradictory and the possible role of maternal HBV infection in the pathogenesis of pregnancy-related outcomes remained unresolved. A study suggested that higher HBV viral load may be associated with poorer pregnancy-related outcomes [164].

A prospective cohort study from China Mainland suggested that maternal chronic HBV infection was associated with an increased risk of miscarriage [165].

A few studies from China also demonstrated significant associations between maternal chronic HBV infection and low birth weight or small-for-gestational age [166, 167]. However, studies from the U.S. reported no significant association between maternal chronic HBV infection and small-for-gestational age [168, 169].

For gestational diabetes mellitus, a meta-analysis revealed that maternal chronic HBV infection had a 47% increased risk of gestational diabetes mellitus (adjusted odds ratio: 1.47) compared with those without HBV infection [170]. This association might stem from low-grade systemic inflammatory response from HBV infection [171].

For pregnancy-induced hypertension, previous case–control and cohort studies have demonstrated inconclusive results [172, 173]. A recent meta-analysis suggested that maternal chronic HBV infection was associated with 23% decreased risk of pre-eclampsia [174]. However, most of included studies were case–control studies and possible mechanism has not been postulated for this association.

Impact of maternal chronic HBV infection on preterm birth is also inconclusive. A meta-analysis demonstrated no association between maternal chronic HBV infection and preterm labor [175]. However, another recent meta-analysis suggested a significant association between maternal chronic HBV infection and premature birth [176]. Of note, abnormal liver function test and concomitant fatty liver were stronger risk factors for preterm birth than maternal chronic HBV infection in previous study [177]. It is possible that liver inflammation per se plays an important role of preterm birth regardless of maternal chronic HBV infection.

Cohort studies from China Mainland demonstrated that maternal chronic HBV infection was associated with an increased risk of intrahepatic cholestasis of pregnancy [178, 179].

A study from U.S. found that patients with chronic HBV infection were less likely to perform cesarean delivery. However, studies from Asia showed that patients with HBV infection had an increased rate of cesarean delivery. This result might stem from on maternal request or obstetrician's recommendation based on the belief that cesarean delivery reduces mother-to-child transmission [180].

No associations were found between chronic HBV infection and adverse perinatal outcomes, including gestational diabetes mellitus, pre-eclampsia, placenta previa, premature separation of placenta, premature rupture of membranes, preterm birth, and low birth weight in females undergoing assisted reproductive technology [181].

Recommendations

Hepatitis B viral infection in the mother does impact the perinatal and pregnancy-related outcomes both in the mother and the newborn. The maternal effects include miscarriage, gestational diabetes mellitus, pregnancy-induced hypertension, preterm birth, intrahepatic cholestasis of pregnancy, and cesarean delivery. However, the data from available studies are not strong enough to associate these complications to mere HBV infection (B2).

Areas of future research

Whether serum HBV viral load is associated with increased risk of perinatal outcomes in maternal HBV infection should be further investigated.

Impact of pregnancy on hepatitis B virus infection severity and outcomes (acute and chronic) and management of liver disease (general management and use of antivirals) in pregnant females with hepatitis B virus infection

Review of literature

Although the management for patients with acute and chronic HBV infection during pregnancy is similar to that

of non-pregnant patients, several issues may be considered because of the presence of the fetus in pregnant patients. These will be addressed under different scenarios described below.

There is scarcity of reports on acute hepatitis B infection in pregnancy; however, it seems that the clinical course is not differ from non-pregnant state [131], and hence, the management would mainly be supportive. The usual disease course would likely be uneventful. Under a very rare circumstance, when fulminating hepatitis occurs, the management decision would be made with the considerations of the chance of spontaneous liver function recovery in the mother and the degree of fetus maturity. As such, liver transplantation and early fetal delivery may be contemplated accordingly.

Obstetricians sometimes would manage chronic HBV-infected patients with pregnancy for pregnancy-related liver problems and hepatitis B virus-related problems, both of which, in particular, the latter would involve the management by hepatologists. The most common liver problem in pregnancy is HBV flares. Incidence of HBV flare and hepatic decompensation has been studied in a large retrospective study recruiting 310 chronic HBV-infected patients with pregnancy (19 received nucleos(t)ide analogs (NA) before pregnancy; 16 received NA during the first or second trimesters; 5 during the third trimester) [182]. ALT flares [defined by $\geq 2\times$ upper limit of normal (ULN)] occurred in 14% during pregnancy and 16% within 6 months of delivery. ALT flares $\geq 5\times$ ULN or $\geq 10\times$ ULN occur in $\leq 5\%$ during pregnancy or postpartum period. Overall, 12% of patients with ALT flares developed jaundice and 2% [2 patients (1 with pre-existing cirrhosis)] developed hepatic decompensation. According to another study with 158 pregnant females, ALT flares developed in 3.4% during pregnancy and 4.3% after delivery [136]. No flares were severe and no liver decompensation was observed. As mentioned above, ALT flares can also occur during the postpartum period. According to one study ($n=317$), postpartum ALT flares $>2\times$ ULN and >5 X ULN occurred in 9.8% and 1.9% in CHB mothers [183]. Another study with 126 patients reported 25% chance of postpartum ALT flares which usually resolved spontaneously [184]. Acute-on-Chronic liver failure (ACLF) due to HBV reactivation had been reported in a case series of 5 patients (all were non-cirrhotic) and all recovered with antiviral treatment [185]. Rarely happened condition is patients requiring liver transplantation for fulminating hepatic failure due to HBV reactivation [140, 186]. In summary, mild ALT flares during and shortly after delivery are not uncommon, whereas hepatic decompensation is rare.

Although NA treatment would theoretically reduce the chance of ALT flares due to HBV reactivation, whether it should be given routinely would depend on the different scenarios.

Patients who are already on long-term NA therapy before conception

In the patients who are already on long-term NA therapy before conception, the question would be whether the treatment should be stopped once pregnancy is planned or confirmed. There are two major considerations in this context: (1) whether NA would increase the risk of fetus anomalies if it is continued throughout the pregnancy and (2) whether discontinuation of NA therapy would jeopardize the liver condition of the mothers and if in case becoming severe, adversely affects the fetus. To date, on one hand, there are no prospective control studies to compare the mother and fetus outcome between those continue and those discontinue NA therapy. On the other hand, there is absence of evidence on the hypothetical chance of teratogenic effects of the HBV treatment continuation that we could learn from the experience from HIV pregnancy registry. According to the Antiretroviral Pregnancy Registry, of the 11 867 females on anti-retroviral therapies for HIV and/ or HBV infection, the rate of birth defects was 2.7% which is very similar to the rate (2.72%) in the general population [187]. Among the NAs, tenofovir disoproxil fumarate (TDF), lamivudine (LAM), and telbivudine (LdT) have been assessed as providing good maternal and infant safety [188, 189].

Among the currently available NAs, LdT and TDF are classified as category B drugs (no risk in animal studies, but unknown in humans), whereas LAM, adefovir (ADV), and entecavir (ETV) are classified as category C drugs (teratogenic in animals, but unknown in humans) by the US FDA. Category B NAs (LdT and TDF) may be considered for mothers needing antiviral treatment during the first through third trimester of pregnancy.

As LAM and LdT have low genetic barriers that may lead to the emergence of drug-resistant strains of HBV [190], TDF should be the first choice for pregnant females. If the pregnant female has impaired renal functions or osteoporosis, LdT or LAM can be used [191, 192]. ETV and ADV should be avoided in females with pregnancy intention, because these drugs have potential serious adverse effects or teratogenesis [191]. If these drugs have been taken before pregnancy, it should be changed to TDF [192].

The newly approved tenofovir alafenamide (TAF) has been recommended for CHB treatment in many parts of the world owing to its better renal and bone safety profile compared to TDF. However, there are limited data on the use of TAF in pregnancy, while it is not recommended during breastfeeding [193].

Concerning the effect on the liver if treatment is stopped, it is well known that around 40–50% of non-pregnant chronic HBV-infected individuals would have ALT flares after NA cessation [194], with majority of the events happening within the first-year treatment cessation. In the context of

chronic HBV-infected patients with pregnancy, according to a study, 8 (6 of those had fivefold increase in ALT levels) out of 12 patients would experience ALT flares after stopping NA treatment during pregnancy [195]. According to another study, ALT flares occurred in 31% of patients who stopped NA during the first trimester (16% of patients who stopped NA before pregnancy) [196]. Cases of acute exacerbation of HBV with liver failure that eventually required urgent liver transplantation have been reported [140, 186].

There are two factors in pregnancy which would enhance the chance of ALT flares postpartum after treatment cessation. First, pregnant females are relatively younger and, therefore, more immune active. They are expected to have a higher chance of HBV reactivation upon treatment cessation. Second, it is known that pregnancy induces immune suppressive state in the mothers to reduce fetal rejection. Together with the increased cortisol, estrogen, and progesterone levels, it creates a potential favorable condition for the HBV to replicate. One study had demonstrated an increase in HBV DNA levels and a decrease in ALT levels during pregnancy, while these profiles reversed after pregnancy [197]. However, another study found that HBV DNA levels during pregnancy were highly variable with some patients having a rise in third trimester or postpartum period, while majority of patients having static HBV DNA levels throughout the pregnancy [198]. Further to these findings, a recent study had shown that pregnant CHB patients had a shift toward Th1 response over Th2 during peripartum period with the host immunologically attempting to clear the virus [199], although it usually fails. At the same time, cortisol levels would decrease immediately after delivery enhancing a steroid withdrawal effect [137].

These combined factors would increase the chance of HBV reactivation, especially during the later course of pregnancy and early course after delivery. Taken all the above findings and considerations together, it is recommended that NA would better to be continued throughout the pregnancy and early postpartum to avoid uncontrolled HBV reactivation. This recommendation would be much stronger in patients with advanced fibrosis/cirrhosis. It is because severe flares, maternal mortality, and fetal death occur in 15%, 1.8%, and 5.2%, respectively, after treatment cessation according to a retrospective study of 400 pregnant females with HBV-related cirrhosis [200].

If a woman was planning pregnancy or a pregnant chronic HBV-infected mother was taking the NA of FDA-defined pregnancy category C drugs, it is recommended to switch to a FDA-defined pregnancy category B drugs.

Treatment naïve chronic HBV-infected patients who become pregnant

The second scenario applies in treatment naïve chronic HBV-infected patients who become pregnant. As mentioned above, HBV reactivation can occur as a result of alteration of immune regulation during and after pregnancy (postpartum). Immune reconstitution during early postpartum period is associated with ALT flares and hence increased HBeAg and HBsAg loss. According to one study, HBV DNA flares (defined by > 2 log IU/mL) and ALT flares (defined by 5 X ULN or 3 X the baseline values) occur in 9% and 6% of patients during pregnancy and 4% and 10% within 3 months of delivery, respectively [201]. Fifty percent of these ALT flares were observed during the second trimester or earlier. According to another study examining 146 pregnant chronic HBV-infected patients not receiving antiviral treatment, the median ALT levels significantly increase from 17 U/L at baseline to 29 U/L at postpartum period [202]. In addition, 7 "immunotolerant" patients developed postpartum ALT flares with the median ALT level of 75 U/L [202]. ACLF due to HBV reactivation has been reported in chronic HBV-infected patients with pregnancy [140]. This is likely due to the natural decline of cortisol levels (usually peaked at term and delivery) during postpartum period mimicking the steroid withdrawal effect. Close monitoring of the HBV DNA and ALT flare profiles during pregnancy and postpartum period for those who are not on NA throughout the pregnancy is recommended. This monitoring should be extended till 6 months post-delivery. If the severe ALT flares are evidenced, prompt initiation of NA treatment should be implemented.

Portal hypertension in chronic HBV-infected females with established cirrhosis

Another issue is management of portal hypertension in chronic HBV-infected females with established cirrhosis. These patients usually have a relatively lower chance of conception because of two reasons. First, they are relatively older. Second, patients with liver cirrhosis would have hypothalamic–pituitary dysfunction and disturbed sex hormone metabolism [203], both of which would adversely affect fertility. Because of this, the incidence of cirrhosis in pregnant females is found to be very low with approximately 1 in 5950 pregnancies [204]. Nonetheless, in chronic HBV-infected pregnant patients with cirrhosis, portal hypertension may be exaggerated during pregnancy due to the normal physiological changes associated with pregnancy. These include increase in blood volume, increase in heart rate, and decrease in systemic vascular resistance. It has been shown that MELD score is predictive for significant liver-related complications during pregnancy [205] In particular,

MELD > 10 is highly sensitive and specific for predicting liver decompensation during pregnancy [205].

For patients with compensated cirrhosis and with a plan for pregnancy, screening for varices is required before pregnancy and preventive measure for acute variceal bleeding, e.g., endoscopic ligation is required. Acute variceal bleeding with catastrophic outcomes can occur during pregnancy in 18–32% of these patients [206] with the mortality rate of up to 50% [207]. It usually occurs during the second trimester or during delivery. It is more related to the gravid uterus and to repeated Valsalva maneuvers [208]. It is recommended to perform endoscopy surveillance with endoscopic ligation for medium- and large-sized varices during the second trimester in patients even with the absence of varix in the first screening before pregnancy. This procedure is safe and effective in preventing acute variceal bleeding. If bleeding risk is assessed to be high (in patients with large varices), non-selective beta blocker may be considered [209]. Close fetal monitoring is necessary for the possibility of fetal bradycardia and intra-uterine growth retardation. Nevertheless, overall, propranolol therapy appears to be quite safe for pregnancy. The use of vasopressin (may also be applicable to octreotide) is, however, contraindicated because of the decrease in placental perfusion and increased risk of placental abruption [210]. Several successful cases with the use of transjugular intrahepatic portosystemic shunt (TIPS) have been reported [211]. Worsening of ascites with compromised respiratory function has also been reported in these patients [212].

Patients with stable chronic HBV disease undergoing prophylactic treatment to prevent mother-to-child transmission

The final scenario is patients with stable chronic HBV disease undergoing prophylactic treatment to prevent mother-to-child transmission based on the high HBV DNA levels (> 200,000 IU/mL) [see below].

Recommendations

Acute hepatitis B infection in patients with pregnancy usually requires specialized supportive treatment (weak recommendation, moderate-quality evidence); and if severe and progressive, urgent liver transplantation may be needed. Early termination of pregnancy and early fetal delivery are rarely required (B2).

For females already on NA treatment before pregnancy with established advanced fibrosis/cirrhosis, continuation of the NA treatment throughout the pregnancy is highly recommended (B1).

For females already on NA treatment before pregnancy with less-advanced fibrosis, continuation of NA treatment during pregnancy should be considered (C1).

During pregnancy, switching from FDA classified pregnancy category class C to class B should be considered. TDF is recommended as the first choice antiviral for pregnant females (B1).

For chronic HBV-infected females who were not eligible for antiviral treatment, and are thus treatment-naïve at the time of pregnancy, HBV DNA and ALT levels monitoring are mandatory throughout the pregnancy, and up to 6 months after pregnancy, treatment is indicated with significant flares (B1).

Pregnant females with chronic HBV infection and established cirrhosis and with a plan for pregnancy should undergo a surveillance endoscopy to screen to varices; prophylactic variceal management is recommended before pregnancy (C1).

For pregnant females with cirrhosis, it is recommended to perform endoscopy surveillance with endoscopic ligation for medium- and large-sized varices during the second trimester in patients even with the absence of varix in the screening before pregnancy (C1).

Areas of future research

Whether or not to continue NAs in females already on NA treatment before pregnancy and with less-advanced fibrosis requires further studies.

Whether to start NA in pregnant females who before getting pregnant were not eligible for anti-HBV therapy needs further studies.

More data on TAF safety in pregnancy are needed.

Mother-to-child transmission (MTCT) of hepatitis B virus [mechanisms and associated factors]

Review of literature

Mother-to-Child Transmission (MTCT) of HBV refers to the entry and replication of maternally derived HBV in offspring to produce novel virions. MTCT of HBV is a major cause of chronic HBV infection. Before the availability of hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine, MTCT of HBV occurred in 70–90% of the children born to HBsAg- and HBeAg-positive mothers and 10–40% of those born to HBeAg-negative mothers. With the administration of HBIG and hepatitis B vaccine, MTCT rates in children of HBeAg-positive and HBeAg-negative chronic HBV-infected mothers have been reduced to 4–10% and < 0.1%, respectively [213, 214]. MTCT of HBV is considered to occur

during ante-partum (in utero), intra-partum (during labor and delivery), or postpartum (after birth) period.

HBV in utero transmission

In utero transmission of HBV refers to the replication of HBV in fetal hepatocytes before birth. Although it is considered that HBV DNA may integrate in ova and granular cells and HBV may infect embryos [215], the findings that the neonatal immunoprophylaxis protected against MTCT of HBV in almost all infants born to HBeAg-negative mothers [213, 214], or born to HBeAg-positive mothers who received oral antivirals during the third trimester of pregnancy [216, 217] indicate the unlikelihood of HBV in utero transmission through infection of embryos.

The presence of HBsAg and/or HBV DNA in umbilical or peripheral blood samples collected shortly after birth was presumably considered to be a consequence of in utero transmission [218, 219]; this was also assumed to be the main reason for MTCT of HBV after passive–active immunoprophylaxis (i.e., immunoprophylaxis failure) [220]. However, longitudinal observations showed that most of infants with positive HBsAg and/or HBV DNA at birth were not HBsAg positive in the follow-up [221, 222]. Thus, the presence of HBsAg or HBV DNA at birth just indicates exposure to, but not infection with HBV [222].

As a general rule, the prerequisite for in utero transmission of a microbial pathogen is that it can cross placentas. However, HBV is not cytopathogenic and there is no evidence for placental damage caused by HBV. Theoretically, placental barrier may prevent the entry of HBV into fetus. The findings that acute hepatitis B occurring in the first or second trimester of pregnancy rarely caused HBV infection in infants indicate that the virus does not easily cross the placenta [223]. The lack of anti-HBc IgM in newborn infants of HBV-infected mothers also suggests little in utero transmission [224].

To date, there are no practicably available ways to define HBV in utero transmission. As aforementioned, the presence of HBsAg and/or HBV DNA in umbilical cord blood or infants shortly after birth cannot be used to define in utero transmission [221, 222]. It is generally accepted that persistence of positive HBsAg from birth to several months of age can define in utero transmission [225]; however, the measurement of HBV markers was performed at intervals of one or more months and the dynamic changes of HBsAg or HBV DNA levels during these intervals were unknown. Because the maternal HBsAg in infants may remain for more than 1 month [226] and seroconversion of HBsAg may be detected 4–5 weeks after inoculation of HBV in experimentally infected chimpanzees [227], it is possible that, if newborn infants are infected during intra-partum period, they may actively produce viral markers before the disappearance of maternally derived HBsAg and/or HBV, leading to the persistence of HBsAg in circulation. Thus, the reported persistence of HBsAg and/or HBV DNA at intervals of 1 month or more does not necessarily mean true in utero transmission, and the possibility of transmission occurred during intra-partum period cannot be excluded.

In summary, MTCT of HBV by in utero transmission, if really occurs, should be very rare. More convincing evidence is required to demonstrate HBV in utero transmission.

HBV intra-partum transmission

HBV intra-partum transmission refers to the entry of maternal HBV in newborn infants during labor and/or delivery and, subsequently, the replication of HBV in infants. The vast majority of MTCT of HBV occurs during the intra-partum period. Maternal blood can cross placenta during labor [228]. After starting the first stage of labor, the repetitive and strong contractions of the uterus may cause maternal–fetal microtransfusion or transplacental leakage, leading to the entry of maternal HBsAg and HBV into expectant infants, which may explain the presence of HBsAg and/or HBV DNA in > 30% of infants at birth [221, 222]. During the second stage of labor, an infant directly comes in contact with maternal HBV-containing body fluids, during which maternal HBV may enter into newborn infants through obvious or imperceptible lesions of skin and/or mucosa. Thus, all infants born to HBsAg-positive mothers, regardless of HBeAg state or HBV DNA level, inevitably undergo exposure to maternal HBV.

In addition, before the availability of immunoprophylaxis, MTCT of HBV occurred in 70–100% of infants born to mothers who had acute hepatitis B near delivery [229], but rarely occurred in infants born to mothers with acute hepatitis B occurred during the first or second trimester of pregnancy [223]. The reason is likely that the mothers with acute hepatitis B around delivery might have high viral load at delivery, which is a main risk factor for MTCT of HBV, whereas the mothers with acute hepatitis B at the first or second trimester might have resolved the infection or might have low viral level at delivery.

HBV postpartum transmission

In the era of no immunoprophylaxis against hepatitis B, postnatal transmission of HBV from HBsAg-positive mothers to their offsprings occasionally occurred because of the close contacts. With the universal vaccination against hepatitis B in all infants and administration of HBIG in infants of HBsAg-positive mothers as well, postnatal transmission of HBV rarely occurs. Theoretically, HBV may be transmitted through breastfeeding, because HBV can be detected in breast milk and nipple cracks may occur during

breastfeeding. However, studies showed that breastfeeding does not have additional risk for infection in infants [see below].

Risk factors for MTCT of HBV

Maternal HBV DNA level and HBeAg state: Maternal high HBV DNA level (viral load) is a main risk factor for MTCT and immunoprophylaxis failure. Studies showed that maternal HBV DNA levels that may cause immunoprophylaxis failure are somewhat varied, ranging from $> 2 \times 10^5$ IU/ml or $> 2 \times 10^6$ IU/ml measured with commercial reagents made in China Mainland [221, 222], $> 10^7$ IU/ml tested with Abbott Real-Time HBV DNA assay [230], to $> 2 \times 10^7$ IU/ml (10^8 copies/ml) detected with Roche reagents [214]. A meta-analysis was done by WHO to assess the risk of perinatal infection according to the maternal HBV viral load (measured by log10 IU/mL) among infants who received a timely birth dose and HBIG. Studies with a small sample size (< 10 subjects) were excluded. When timely birth dose and HBIG were used, there was no breakthrough infection reported when the maternal HBV DNA viral load was below 5.3 $\log_{10}$ IU/mL (200,000 IU/mL) [231]. Therefore, it is generally accepted to use HBV DNA $\geq 2 \times 10^5$ IU/ml as a threshold for risk of MTCT after the immunoprophylaxis [192, 231, 232].

HBeAg-positive individuals have higher HBV DNA levels.

In Asia, the median HBV DNA levels in HBeAg-negative chronic HBV-infected pregnant females are approx 3–4 $\log_{10}$ IU/ml, and the proportion of $> 10^6$ IU/ml is only 0.5–1.8%, while the HBV DNA levels in HBeAg-positive pregnant females are > 7 $\log_{10}$ IU/ml and the proportion of $> 10^6$ IU/ml or $> 10^6$ copies/ml is over 80% [98, 233]. Immunoprophylaxis failure occurs in < 0.1% of children born to HBeAg-negative mothers, but in 4–10% of children born to HBeAg-positive mothers [213, 214]. Thus, the presence of HBeAg in pregnant females indicates the risk of MTCT even after immunoprophylaxis. Meta-analysis by WHO to assess the performance (sensitivity and specificity) of HBeAg tests in pregnant female with HBV infection in identifying female with high HBV DNA levels ($\geq$ 5.3–6.2 $\log_{10}$ IU/mL), found good sensitivity [88.2% (95% CI 83.9–91.5)] and specificity [92.6% (95% CI 90–94.5)] of HBeAg for diagnosis of HBV viremia $\geq$ 5.3–6.2 $\log_{10}$ IU/mL [231]. For predicting the risk of mother-to-child transmission, HBeAg had high sensitivity [99.1% (95% CI 61.8–100)], but low specificity [55.7% (95% CI 34.0–75.5)]. When restricted to children receiving birth dose vaccine plus HBIG, HBeAg had a sensitivity of 98.8% (95% CI 52.0–100) and specificity of 49.2% (95% CI 25.1–73.7). Thus, compared to HBV DNA, HBeAg has high sensitivity but lower specificity for predicting the risk of mother-to-child transmission. HBV DNA quantification is the best method to determine eligibility for tenofovir prophylaxis in pregnant females to prevent MTCT. However, HBeAg can be used as an alternative test in settings with limited access to HBV DNA quantification [231].

Time of immunoprophylaxis in newborn infants: Newborn infants of HBsAg-positive mothers are exposed to maternal HBV during labor and delivery; those who are born to mothers with high viral loads are exposed to more amounts of maternal viruses. Theoretically, if the maternal viruses can be completely neutralized by the immunoprophylaxis as well as the neonatal innate immunity before they enter into hepatocytes, MTCT will not occur at all. Studies showed that delayed or missed use of HBIG and/or hepatitis B vaccine may increase the likelihood of MTCT [234, 235].

Recent studies showed that, after early (within 1 h after birth) administration of HBIG and hepatitis B vaccine, MTCT of HBV in infants born to HBeAg-positive mothers was reduced to 1.2–2.4% [236], much lower than reported rate of 4–10% in infants who received recommended immunoprophylaxis within 12 or 24 h after birth[213, 214]. Thus, timely administration of the immunoprophylaxis in newborns is critical for preventing MTCT of HBV.

Other risk factors for MTCT of HBV: Recently, it has been proposed that quantification of HBsAg may predict MTCT of HBV [237, 238]; however, this is controversial [239].

Investigations on the association between HBV genotypes or mutations in the 'a' determinant of S gene and MTCT remain inconclusive [240].

In addition, studies on the issue of whether cesarean section may reduce MTCT of HBV showed conflicting results [see below].

Recommendations

MTCT of HBV mainly occurs during labor and delivery. The rate and timing of intra-uterine transmission is not well known and requires further studies (B2).

Known risk factors for MTCT are high maternal HBV DNA level or positive HBeAg status, and suboptimal use of HBIG and/or hepatitis B vaccine after birth. (A1).

Areas of future research

More studies on searching convincing evidence of in utero transmission are needed.

Whether quantification of HBsAg may predict MTCT of HBV needs to be studied.

The effect of cesarean section in preventing MTCT in females with high viral load or positive HBeAg if they do not receive antivirals during the trimester of pregnancy.

Prevention of mother-to-child transmission

Review of literature

Mother-to-child transmission (MTCT) of HBV is the leading mode of transmission in endemic populations [231]. The infected children of HBV-infected mothers become a reservoir of infection for subsequent horizontal infection in the community, and the HBV infected females in turn continue maternal-to-infant transmission to their descendants. The prevention of MTCT is the most effective mean of interrupting this vicious cycle, reducing the prevalence of HBV infection in successive generations [241].

Immunoprophylaxis and prevention of MTCT

Without any intervention, MTCT of HBV is 70–90% if mother is HBsAg-positive and HBeAg-positive; and 10–30% if mother is HBsAg-positive only [241]. Timely hepatitis B vaccination birth dose (HepB birth dose) alone is 70–95% effective in preventing MTCT [241–243]. Timely HepB birth dose plus the completion of hepatitis B vaccine series is > 95% effective in preventing MTCT [242].

Thus, all infants should receive the first dose of hepatitis B vaccine as soon as possible (preferably within 24 h) after birth, followed by completion of the vaccination series. In the case of preterm babies, the birth dose should be given even if the baby weight is < 2 kg, but should be followed by a further three vaccine doses starting at 6 weeks of age [244]. This is because the hepatitis B vaccine has reduced immunogenicity in preterms with < 2 kg weight [245].

Many studies including Cochrane systematic reviews indicate that combination of Hepatitis B vaccine with HBIG is more efficient in reducing MTCT prevalence than vaccine or HBIG alone [246, 247].

One systematic review found that 200 IU HBIG had equivalent effectiveness to 100 IU HBIG in infants born to HBsAg-positive mothers for preventing HBV infection [relative risk: 1.08, (0.64–1.82)] and HBeAg-positive mothers [relative risk: 0.84 (0.39–1.77)] [248].

Although a combination of HBV vaccine plus HBIG is the optimum strategy to prevent HBV infection in babies of HBsAg-positive mothers, utility of addition of HBIG to vaccine in babies of HBeAg-negative mothers is unclear. One recent meta-analysis concluded that HBV vaccine alone is equally effective to vaccine plus HBIG for neonates of HBeAg-negative chronic HBV-infected mothers in preventing MTCT of HBV infection [249]. In full-term neonates born to HBeAg-negative chronic HBV infected mothers, protection against MTCT of HBV infection achieved by timely HBV vaccination may not be significantly improved by additional HBIG use [231]. Moreover, due to cost, supply, and safety issues, HBIG use may not be feasible in many regions. It has been shown that HBV vaccine without HBIG has a protective efficacy of 70–95% in HBeAg-positive chronic HBV-infected mothers also [250]. These findings support the use of hepatitis B vaccine alone in settings where use of HBIG is not feasible. Very recently, it was reported that a free-immunoglobulin alternative strategy using HBeAg RDT/ALT algorithm to assess eligibility for TDF prophylaxis associated with an early vaccination in delivery room could reduce HBV MTCT to 1.48% [95% CI 0.40–3.74] for TDF-eligible pregnant female, 0% [95% CI 0–1.41] for those treated more than 1 month, and to 1.06% [95% CI 0.39–2.30] for not TDF-eligible female [251].

Antiviral therapy for the prevention of MTCT

Antivirals can be useful in HBsAg-positive pregnant female as an additional measure to prevent MTCT of HBV. A WHO-commissioned systematic review and meta-analysis (included 129 studies) found that antivirals had protective effect in preventing MTCT [TDF 300 mg: odds ratio (OR) 0.16, 95% CI 0.10–0.26; lamivudine 100 mg: OR 0.17, 95% CI 0.13–0.22; and telbivudine 600 mg: OR 0.10, 95% CI 0.08–0.13]. TDF has a high barrier to drug resistance, and should be the first choice.. All studies in the meta-analysis included HBIG in both trial arms (except six studies, in which the use of HBIG was not reported) [231]. Another systematic review and meta-analysis on 7463 studies also concluded that peripartum antiviral prophylaxis is highly effective, specifically TDF, for the prevention of HBV MTCT [252].

Also there was no adverse effects of maternal TDF prophylaxis on infant bone mineral density at 1 year of age [231].

The maternal HBV DNA levels above which maternal NAs treatment should be started for preventing MTCT is ≥ 200,000 IU/mL or ≥ 5.3 $\log_{10}$ IU/mL. HBV DNA quantification is the best method to determine eligibility for TDF prophylaxis in HBsAg-positive mothers for prevention of MTCT. However, HBeAg can be used as an alternative test in settings with limited access to HBV DNA quantification [231].

HBeAg RDTs could also represent an option to identify females at risk of transmission [253]. The overall sensitivity of identifying high viremia with RDTs is lower as compared to the laboratory enzyme immunoassay techniques [254]. Nevertheless, their possible use in decentralized areas is a major advantage for many countries in the region where it is not possible to have access to enzymatic techniques or viral load quantification outside the capital city.

In many countries, HBeAg-negative chronic HBV infections are common. HBeAg-negative chronic HBV infection is characterized by the lack of serum HBeAg, persistent or fluctuating moderate to high levels of serum HBV DNA

and fluctuating or persistently elevated ALT values, mainly because of mutations in the basal core promoter (BCP) and precore (PC) genes responsible for down-regulation of HBeAg production. Adding ALT measurement for HBeAg-negative pregnant females could represent an option to identify pregnant female with HBeAg-negative chronic hepatitis B at risk of high HBV DNA as reported in Cambodia [255].

Recently, it has been proposed that quantification of HBsAg may predict MTCT of HBV [237, 238]; however, others reported different results [239]. HBsAg level > 4.0 $\log_{10}$ IU/mL has been suggested as a cut-off to start antiviral prophylaxis to prevent MTCT of HBV [237], as high maternal HBsAg level has been associated with higher risk of HBV immunoprophylaxis failure in some studies [238]. However, the correlation of HBsAg level with maternal HBV DNA level was not found in many studies [239]. Further prospective studies are needed before introduction of HBsAg quantification as a reliable test in pregnant females for eligibility of maternal NAs prophylaxis to prevent MTCT of HBV [215].

Varying schedules have been suggested to start and stop peripartum antiviral prophylaxis, ranging from starting at 24–28 to 28–32 weeks of gestation, and from stopping at delivery to 12 weeks postpartum [192, 231]. The WHO meta-analysis found that effectiveness of TDF prophylaxis for preventing MTCT was similar irrespective of the timing of start of TDF: TDF prophylaxis starting at < 28 weeks (OR 0.10, 95% CI 0.04–0.25), 28 weeks (OR 0.24, 95% CI 0.13–0.44), or > 28 weeks (OR 0.09, 95% CI 0.02–0.32) [231]. Some studies suggest that earlier start of NAs, i.e., in the second trimester, might be more efficacious than in the third trimester as this might lead to greater viral load reduction in females treated earlier [252]. A Bayesian network meta-analysis and system review showed that the risk of MTCT decreased significantly in pregnant females accepting intervention before 28 weeks of gestation, as compared to those initiating after 28 weeks [relative risk: 0.019, (0.00034–0.19)] [256]. In the recent PROHM study, HBV transmission rate was 6.52% [1.37–17.9] for those treated less than 1 month as compared to 0% [95% CI 0–1.41] for those treated more than 1 month [251].

There has been some concern that NA (used for MTCT prevention only) withdrawal at or after delivery might increase the risk of postpartum flares [197]. The WHO meta-analysis found that 8% of the mothers receiving TDF during pregnancy experienced a flare after discontinuation, compared with 6% of mothers who did not receive TDF at a matched time-point. This suggests that discontinuation of TDF prophylaxis might not increase the risk of flare [risk difference: 0.00 (95%CI 0.04–0.04)] [231]. Most flares are mild and self-limiting; only a few require antiviral therapy [184, 257]. Another meta-analysis found similar rate of hepatitis flare among mothers discontinuing antiviral treatment immediately after delivery, 4 weeks postpartum, and 12 weeks postpartum [258]. Thus, HBsAg-positive pregnant females receiving antivirals for MTCT prevention can discontinue antiviral treatment immediately after delivery or continue up to 12 weeks postpartum. HBV DNA could rebound after antiviral discontinuation; close monitoring should be done and antiviral treatment can be considered if meeting treatment indications for therapy [259].

One study found that 6 weeks postpartum is the peak period of hepatitis flares, and 96.0% of the hepatitis flares occurred within 24 weeks postpartum. Therefore, follow-up to at least 24 weeks postpartum after discontinuation of antivirals (used for MTCT only) should be done [260]. One study on chronic hepatitis B virus-infected females who received telbivudine beginning at week 24 or 28 of gestation and followed up to 52 weeks postpartum found that, compared with female having a normal ALT level throughout pregnancy, those with elevated ALT had a significantly higher rate of ALT flare after telbivudine withdrawal (25.0% vs 11.9%; $p = 0.039$). And females with elevated ALT during pregnancy who continued antiviral treatment to 52 weeks postpartum had a significantly higher HBeAg seroconversion and decline in HBsAg levels [261]. Thus, pregnant females with ALT flares during pregnancy should undergo monitoring and continue long-term antiviral treatment after delivery, and stopping rules as per guidelines for other chronic HBV-infected patients should be followed. Females with evidence of advanced liver fibrosis/cirrhosis should also continue long-term antiviral treatment after delivery, and stopping rules as per guidelines for other chronic HBV-infected patients should be followed [259].

Recent studies have found that children with and without fetal exposure to TDF during late pregnancy to prevent maternal transmission of HBV had comparable long-term growth, renal function, and bone development, assessed by serum bone metabolism markers and DXA scans, up to 6–7 years of age [262].

Recommendations

All newborns should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 h. The birth dose should be followed by three doses to complete the primary series (A1).

HBIG prophylaxis, in conjunction with HBV vaccination, may be of additional benefit for newborn infants whose mothers are HBsAg positive and also HBeAg positive. In full-term neonates born to mothers who are HBsAg positive but HBeAg negative, protection against perinatally acquired infection achieved by immediate vaccination against HBV (given within 24 h) may not be significantly improved by the addition of HBIG (B1).

Pregnant females testing HBsAg positive with an HBV DNA ≥ 5.3 log10 IU/mL (≥ 200,000 IU/mL) should receive antiviral prophylaxis for prevention of mother-to-child transmission of HBV. This is in addition to appropriate immunoprophylaxis (B1).

In settings in which antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for tenofovir prophylaxis to prevent mother-to-child transmission of HBV (B2).

Tenofovir disoproxil fumarate (TDF) is recommended for pregnant females with HBV requiring antiviral prophylaxis for prevention of mother-to-child transmission of HBV (B1).

The antiviral should be initiated at 24–28 weeks of gestation for preventing MTCT. For pregnant females with high viremia who are visiting the hospital after 28 weeks of gestation, antiviral intervention should be initiated immediately. The pregnant mothers should be made aware of the intra-uterine risk of HBV transmission, even with low HBV DNA levels, and can be given a choice of starting antiviral therapy from the first trimester of pregnancy (C2).

Pregnant females taking antivirals for preventing MTCT only can discontinue antiviral treatment immediately after delivery or continue up to 12 weeks postpartum (C2), and should be monitored closely for hepatitis flare and rebound of HBV DNA till at least 24 weeks (C2).

Pregnant females with ALT flares during pregnancy or evidence of advanced liver fibrosis or cirrhosis should continue long-term antiviral treatment after delivery, and stopping rules as per guidelines for CHB patients should be followed (C1).

Follow-up to at least 24 weeks postpartum after discontinuation of antivirals (used for MTCT only) should be done (C1).

Areas of future research

Use of HBsAg level and HBeAg testing as a cost-effective alternative to HBV DNA viral load measurement to determine eligibility for antiviral prophylaxis for MTCT of HBV needs to be studied.

When to stop antivirals after delivery in female and how to follow up such females remain to be studied.

Data regarding the maternal and infant safety of TAF in pregnant females with chronic hepatitis B and the efficacy to prevent MTCT of hepatitis B need to be generated.

Development of RDTs for HBeAg with higher diagnostic accuracy, and evaluation of the performance of HBeAg tests in the presence of co-infection with HIV, HCV, and HDV and in different genotypes are needed.

Safety of invasive obstetric procedures in the pregnant females with hepatitis B virus infection in terms of mother-to-child transmission and optimum mode of delivery in HBsAg-positive mother

Review of literature

Invasive procedures during pregnancy such as amniocentesis, chorionic villus sampling, fetal blood sampling, and minimally invasive or open fetal surgery can contribute to MTCT and immunoprophylaxis failure in the newborns. Thus, appropriate management during these invasive procedures is important to minimize the MTCT risk.

Studies have found that amniocentesis is an independent factor for the intra-uterine transmission of HBV [263, 264]. In one case–control study on infants who were born to HBsAg-positive mothers without antiviral exposure and completed appropriate immunization, it was found that there were no significant differences in the vertical transmission rates between the amniocentesis group and the control group if the maternal HBV DNA levels were < 6.99 log10 copies/ml. However, among mothers with HBV DNA levels ≥ 7 log10 copies/ml ($\geq 2 \times 10^6$ IU/ml), a significantly higher vertical transmission rate was seen in the amniocentesis group vs. the control group (50% vs. 4.5%, respectively, $p = 0.006$) [263]. In a recent large retrospective study, 143 HBsAg-positive females with amniocentesis were compared with 605matched (based on maternal viral loads, antiviral therapy regimens, and delivery dates) non-amniocentesis cases. Pregnant females with serum HBV DNA ≥ 1.0×10^6 (6.0 log10) IU/ml were offered antiviral therapy. MTCT rate was significantly higher in the females undergoing amniocentesis as compared to those not undergoing amniocentesis (2.80% vs. 0.50%; RR, 5.64, 95% CI 1.28–24.93). In the amniocentesis group, maternal HBV DNA ≥ 7.0 log10 IU/ml and HBeAg positivity were associated with higher MTCT rates; and antiviral therapy reduced MTCT rate from 14.3 to 0% ($p = 0.554$) when maternal HBV DNA was ≥ 7.0log10 IU/ml [265]. Thus, for HBsAg-positive mothers planned for invasive procedures such as amniocentesis, counseling should include the risk of MTCT of HBV if the serum HBV DNA is > 7.0 log10 IU/mL [266].

The risk and benefit of antiviral prophylaxis in the prevention of MTCT of HBV in highly viremic pregnant mothers, before or immediately after invasive procedures including amniocentesis, remain largely unknown. Available data were very limited in the literature. Besides, the starting and stopping points of maternal treatment for short-term NAs prophylaxis also remain unclarified.

Non-invasive alternatives should be explored in mothers who require prenatal invasive diagnostic procedures. Among females who need invasive testing, amniocentesis is preferable to chorionic villus sampling. Transplacental amniocentesis should be avoided. The risks and benefits of any invasive procedures should be explained to the patient and informed consent obtained [267].

The major route of perinatal HBV transmission is due to newborn's contact with the HBsAg-positive mother's blood or secretions during delivery. Despite administration of birth dose HBV vaccine plus HBIG, some transmission risk remains for mothers with high HBV DNA levels [See above]. The method of delivery that minimizes the likelihood of MTCT of HBV remains a controversial issue. Recent studies demonstrated a lower risk of HBV transmission with elective cesarean section compared with vaginal delivery. A recent meta-analysis [268] comparing the risk of MTCT of HBV between vaginal delivery versus cesarean section delivery concluded that the risk of HBV infection in cesarean births was significantly lower than that of vaginal delivery in mothers without antiviral prophylaxis during pregnancy. Fortunately at present, for pregnant mothers with high viral load detected during delivery, the risk of MTCT of HBV can be minimized through application of antiviral agent early during third trimester [see above]. Cesarean section should not be performed for the sole indication of reducing risk of vertical HBV transmission.

Recommendations

The risk of intra-uterine HBV transmission in pregnant mothers with high serum HBV DNA level (≥ 7 log10 IU/mL) and planned for invasive genetic testing procedures such as amniocentesis should be discussed with the pregnant mother and relatives; weighing of the benefits and harms is needed (C2).

Cesarean section should not be performed for the sole indication of reducing risk of vertical HBV transmission (C1).

Areas of future research

Further prospective studies on risk factors of HBV transmission in pregnant females undergoing invasive procedures like amniocentesis, and the effect of antiviral therapy on the HBV transmission in such mothers are needed.

Assisted conception in chronic hepatitis B virus-infected females in terms of mother-to-child transmission

Review of literature

Couples seeking help for assisted conception may be infected with chronic hepatitis B virus. They cannot be denied access to the assisted reproductive technology (ART). For many of them, access to such services may be restricted on ethical, geographical, and financial grounds. They may be avoiding unprotected intercourse using condoms to minimize the risk of infecting their partner. The direct threat to their health can be reduced or eliminated by a modification of practices, guidance, and procedures. Assisted procreation may be required for safe conception if the viral infection cannot be effectively treated or if the couple needs fertility treatments because of an infertility diagnosis (e.g., low sperm counts).

Several assisted reproduction procedures, such as in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), are available. Fertility clinics screen patients for blood-borne viral infections, including HBV to prevent vertical transmission and for laboratory safety. From the ethical point of view, there is no reason to advise against assisted reproduction treatment in HBsAg-positive individuals [269]. However, limited access to specialist clinics equipped to cater for these couples and restricted funding may impact negatively couples obtaining risk-reducing assisted reproduction treatment.

Effect of female chronic HBV infection on pregnancy outcomes in assisted reproduction

It has been shown that HBV exists in ovarian tissues (including oocyte and follicular fluid), and can pass the zona pellucida. Therefore, a potential risk of transmission to the embryo exists, which could explain the finding of MTCT despite immunoprophylaxis [270]. In one study, HBsAg was detected in the nuclei and cytoplasm of oocytes and embryos in 6 of 10 HBsAg-negative male/HBsAg-positive female couples (and in 13 of 20 oocytes and embryos) [271]. In another study, the rates of positivity in oocytes and embryos were higher in females with high serum levels of HBV DNA levels; and also in females with HBsAg-positive mothers [272].

Some studies have shown lower rates of fertilization, cleavage, high-quality embryos, and pregnancy in chronic HBV-infected infertile females as compared to non-infected females [273, 274]. Although lower ovarian reserve; and lower rates of fertilization and high-quality embryos have been found in females with HBV DNA levels $\geq 5 \times 10^2$ IU/mL [275], one systematic review showed that among

infertile females with chronic HBV infection undergoing assisted reproduction, there was slightly lower rates of fertilization, but similar rates of cleavage, high-quality embryos, implantation, pregnancy, and abortion, as compared to infertile females without chronic HBV infection [276].

Most studies suggest that the risk of maternal vertical HBV transmission during an IVF procedure is similar to that with spontaneous conception and pregnancy [277–279]. One study on 12 babies born to couples with HBV-positive oocytes and/or embryos found that the presence of HBsAg in oocytes and embryos might not result in the vertical transmission of HBV in the offspring of chronic HBV-infected mothers [279]. A study on 251 HBsAg-positive females (305 children, 176 born with assisted conception, and 129 born with natural conception; 7.5% of children were HBsAg positive at birth), found that HBsAg positivity rate among children at birth was similar in the assisted conception group and the natural conception group (6.3% vs. 9.3%) [280].

Effect of chronic HBV on male fertility and pregnancy outcome

Chronic HBV infection can adversely affect male fertility, specifically sperm count, and progressive motility. HBV exposure could lead to reactive oxygen species generation, lipid peroxidation, reduction of total antioxidant capacity, activation of caspases, and DNA fragmentation, resulting in increased apoptosis of sperm cells and loss of sperm membrane integrity and causing sperm dysfunctions [281]. Results of one study suggested that chronic HBV infection in male was associated with poor sperm quality. There were increased rates of asthenozoospermia and oligozoospermia/azoospermia. The embryo transfer outcomes and clinical pregnancy rates in ICSI cycles were decreased, but do not affect the outcome of IVF [282]. One study reported that the percentage of normal sperm morphology in HBV-seropositive husbands was significantly lower than that of seronegative counterparts (5.0% versus 10.0%, $p = 0.009$). However, there was no adverse effect of chronic HBV infection on the assisted reproduction outcomes [278]. Another study addressing the effect of male chronic HBV infection on outcomes of IVF and embryo transfer treatment included the 215 couples undergoing their first oocyte donation cycles, 19 couples with seropositive husbands/seronegative wives had lower implantation rate, and lower clinical pregnancy rate, but the difference was not statistically significant [283].

HBV can integrate into sperm chromosomes, causing mutagenic effects, and there is the possibility of vertical transmission of HBV via the germ cells [284]. This finding supports the assumption that human sperm cells may act as vectors for the vertical transmission of HBV genes via the germline to progeny [285]. These findings make the sperm washing procedures to remove seminal plasma for reducing the vertical transmission risk debatable. However, the vaccination of female partners against hepatitis B may eliminate the risk of transmission to the mother as well as to the fetus [286].

Microbial contamination of the IVF system

In the embryology laboratory, microbial contamination of the IVF system deserves attention. Cross-contamination of samples is possible within liquid nitrogen storage tanks, since HBV can survive in liquid nitrogen [287]. It can be prevented using sterile techniques and supplementing culture media with screened sera or serum substitutes and antibiotics. Persons whose biological material is to be cryopreserved should be screened for HBV, HCV, and HIV, and separate containers should be used for infected and non-infected material. One study failed to detect viral sequencing from the spent culture media and liquid nitrogen samples of oocytes and embryos from hepatitis B infected females [288].

Recommendations

Assisted reproduction could be done following the same guidelines as in other pregnant females with chronic HBV infection (C2).

Areas of future research

Effect of maternal HBV DNA levels on rate of fertilization, rate of cleavage, quality of embryos, implantation, pregnancy, abortion, and rate of vertical transmission among infertile females with CHBV infection undergoing assisted reproduction requires further large-scale studies.

Postpartum follow-up of children of chronic HBV-infected mothers

Review of literature

Infants should be given appropriate immunoprophylaxis [see above]. Although a combination of active and passive immune prophylaxis is the optimum strategy to prevent HBV infection in babies of HBsAg-positive mothers, its utility in HBeAg-negative mothers is uncertain [see above].

Follow-up of infants born to HBsAg-positive mothers, including the post-vaccination serological testing, is important. Although routine post-vaccination testing is not necessary, it is important for babies born to HBsAg positive, and should be done at 9–18 months of age, 1–2 months after the last dose of HBV vaccine [289].

The post-vaccination serological testing should include HBsAg and anti-HBs titer tests. Passive immunization with

HBIG may result in positive anti-HBs levels before 9 months of age [290]. Adequate protection is indicated by the anti-HBs levels of more than 10 mIU/mL. Revaccination with the entire 3 dose schedule should be done in babies with anti-HBs levels of less than 10 mIU/mL. Babies who are HBsAg positive need appropriate follow-up and management. Anti HBc testing should not be done as it may remain positive up to 2 years of age in babies born to HBAg-positive mothers [290].

More than 95% of healthy newborns respond to a 3 dose vaccine series, and almost all respond to revaccination. However, there are no data regarding the utility of revaccination in babies showing undetectable anti-HBs levels even after 6 HBV vaccine [291].

Recommendations

All children born to HBsAg-positive mothers should be tested at ages 9–18 months for seroconversion (with HBsAg and anti-HBs titers), at least 1 month after the last dose of vaccine (B1).

Areas of future research

Strategies for babies who do not develop protective antibodies even after revaccination need to be studied.

Breastfeeding in hepatitis B virus-infected mothers

Review of literature

Beneficial effects of breastfeeding for the children and the mothers are well known. Besides fostering the close emotional bond through mother-to-infant contact, breastfeeding has been shown to be associated with a significant reduction in hospitalization rates (from gastroenteritis, respiratory infections, and sepsis) in the initial few months after birth; better infant and childhood survival especially in low-resource countries [292, 293]. Prolonged breastfeeding has been associated with improved cognitive function in older children; lower cholesterol levels and body mass index; and lower incidence of obesity and type 2 diabetes among older children and adults [292, 293]. Mothers who breastfeed have shorter recovery time, less anemia (due to oxytocin-stimulated uterus contraction), and reduced risk of obesity, breast cancer, ovarian cancer, and osteoporosis in the long term [294, 295].

Although some older studies had found HBsAg, HBeAg, and HBV DNA in breast milk (both colostral HBsAg and HBeAg titers correlated positively with the corresponding level in maternal blood) [296, 297], clinical studies have failed to demonstrate breastfeeding as a contributor to MTCT of HBV. In a meta-analysis of 10 prospective controlled trials (751 infants in the breastfeeding group and 873 infants in the non-breastfeeding group), there was no significant difference in MTCT of HBV (i.e., infant peripheral blood HBsAg or HBV DNA positivity at age 6–12 months), between the breastfeeding and the non-breastfeeding group [OR: 0.86 (95% CI 0.51–1.45), $p = 0.56$]. The rate of anti-HBs development was also similar between the two groups [OR: 0.98 (95% CI 0.69–1.40), $p = 0.99$). Thus, breastfeeding (without cracked or bleeding nipples or lesions) does not contribute to MTCT of HBV after proper immunoprophylaxis in the infants [298]. The majority of studies were not randomized controlled; and did not study HBV markers in the breast milk or HBV DNA levels in newborns and the mothers. Also, correlation between the rate of MTCT and the duration of breastfeeding has not been studied.

Lactoferrin present in the human milk has antiviral activity against various viruses including HBV, HCV, and HIV [299, 300]. Milk stasis and breast engorgement (resulting from irregular or non-exclusive breastfeeding) have been shown to increase the epithelial permeability, more efficient para-cellular transfer of HIV, and increased HIV RNA in breast milk [301]. Whether the same applies to HBV is unknown. Thus, exclusive breastfeeding needs to be promoted especially in regions with low socio-economic standards, given the beneficial effects of exclusive breastfeeding on morbidity and mortality of the babies.

Another important consideration is the safety of antivirals taken by the breastfeeding mothers for the babies, Among HIV-positive mothers treated with lamivudine 300 mg/day, although the mean concentration of lamivudine in the breast milk was slightly higher (1.8 mg/mL) as compared to that in maternal serum (0.7 mg/mL), the mean concentration of lamivudine was very low in the infant's serum (0.03 mg/mL), indicating minimal absorption of lamivudine in the infants [302]. Although transient and asymptomatic hematological toxicity has been observed in HAART-exposed infants (15.9% neutropenia at 1 month of age vs 3.7% in unexposed group), there were no differences in hematological and hepatic toxicity between breast-fed and formula-fed infants from 2 to 6 months postpartum [303].

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir. After being administered orally, TDF is quickly absorbed from the gut and is converted into tenofovir. As very low level of tenofovir is present in the breast milk and tenofovir also has poor absorption from the GIT, the concentration of tenofovir in infant's blood is very low. Among HIV-infected mothers on long-term treatment including 300 mg oral TDF, very low median tenofovir blood concentrations in the infants have been found (24 ng/ml and 0 ng/ml at 6 and 12 months of age, respectively) [304]. In another study on HIV-positive mothers treated with 300 mg TDF,

none of the infants had a measurable tenofovir concentration in their blood [305].

Tenofovir concentrations in breast milk are also very low. In one study on HIV-infected mothers taking TDF 300 mg daily, median concentration of tenofovir in the breast milk was 5.0 ng/ml at 1 month and 2.5 ng/ml at 12 months postpartum [304]. Another study reported median maximum concentration to be 6.0 ng/ml at 101 days (range 81–146) and 143 days (range 80–125) after delivery [305]. For comparison, the mothers taking TDF at a dose of 300 mg per day, the maternal plasma maximum tenofovir concentration during pregnancy ranged from 245 to 280 ng/ml [306]. Therefore, breast-fed infants experience much lower drug exposure from breast milk [307]. The daily tenofovir dose ingested from breast milk is estimated at 0.4–2.1 µg/kg/day, which represented 0.01–0.04% of the proposed pediatric therapeutic daily dose of 6 mg/kg/day [307]. These data from the HIV-infected mothers can be extrapolated to the HBV-infected mothers, as well. As there is negligible exposure to tenofovir of infants from breastfeeding (of mothers on TDF treatment), breastfeeding should be continued in females receiving TDF.

Tenofovir alafenamide fumarate (TAF), is a new oral prodrug of tenofovir. As compared to TDF, TAF delivers targeted increased intracellular levels of tenofovir, thus reducing the circulating tenofovir exposure. The enhanced safety profile of TAF makes it the ideal antiviral to use in pregnant and breastfeeding HBsAg-positive mothers.

Recommendations

Breastfeeding should be encouraged, as without cracked or bleeding nipples or lesions, breastfeeding does not contribute to MTCT of HBV after proper immunoprophylaxis in the infants (B1).

Breastfeeding should not be contraindicated in females receiving tenofovir for prophylaxis or treatment of HBV, and mothers on TDF treatment should be encouraged to breastfeed (B1).

Areas of future research

If irregular or non-exclusive breastfeeding contributes to increased infectivity of human milk in HBV-infected mothers, needs evaluation.

Anti-HBV effects of components of breast milk, and the mechanisms of no additional risk of MTCT caused by breastfeeding need to be studied.

To properly evaluate the role of breastfeeding in HBV MTCT, more randomized controlled trials with detailed breast milk HBV marker testing and HBV DNA levels in mother/child blood and duration of breastfeeding are needed.

Data on whether a woman on entecavir safely breast feed are lacking.

Figure 1 shows the overall algorithm of maternal and infant management of pregnant females found to be HBsAg-positive first time during HBsAg screening during pregnancy or previously known chronic HBsAg-positive females who become pregnant (and are not on long-term antivirals). Figure 2 shows the overall algorithm of maternal and infant management of previously known chronic HBsAg-positive females who become pregnant and are already on long-term antivirals.

Public health aspects of HBV infection in pregnancy

Review of literature

Hepatitis B is still a major cause of morbidity and mortality due to liver diseases in the Asia–Pacific region. The burden of HBV infection remains disproportionately high in low- and middle-income countries, with most cases occurring from infection acquired soon after birth or during early childhood [308]. The World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis in May 2016, and proposed to eliminate viral hepatitis as a public health threat by 2030 [4]. Elimination is defined as a 90% reduction in incidence and a 65% reduction in mortality, compared with the 2015 baseline. The prevalence of HBsAg in children under 5 years of age is considered a surrogate indicator of the cumulative incidence of chronic HBV infections, and reduction in the prevalence of HBsAg in children under 5 years to < 0.1% by 2030 is one of the global targets [4]. Other global targets for 2030 include 90% coverage of timely HepB birth dose vaccination and 90% coverage of HepB3 [4].

WHO had recommended to include the hepatitis B vaccine in the Expanded Programme on Immunization (EPI) in 1992 [309]. In 2017, the latest update of the WHO position paper recommended for the universal immunization of infants (with three or four doses of hepatitis B vaccine), and giving the first dose of hepatitis B vaccine within 24 h after birth [310]. The birth dose of hepatitis B vaccine should be given as early as possible. If the immunization service is not located in the same health facility (like private clinics, home delivery), it could delay the first vaccine injection, as reported in Cambodia [311]. Injection of the first dose of vaccine just after birth in delivery room could be an effective public health measure by avoiding missed opportunities. Universal immunization of infants with hepatitis B vaccine, including a timely birth dose, is the most effective intervention to prevent MTCT. Other interventions to reduce MTCT

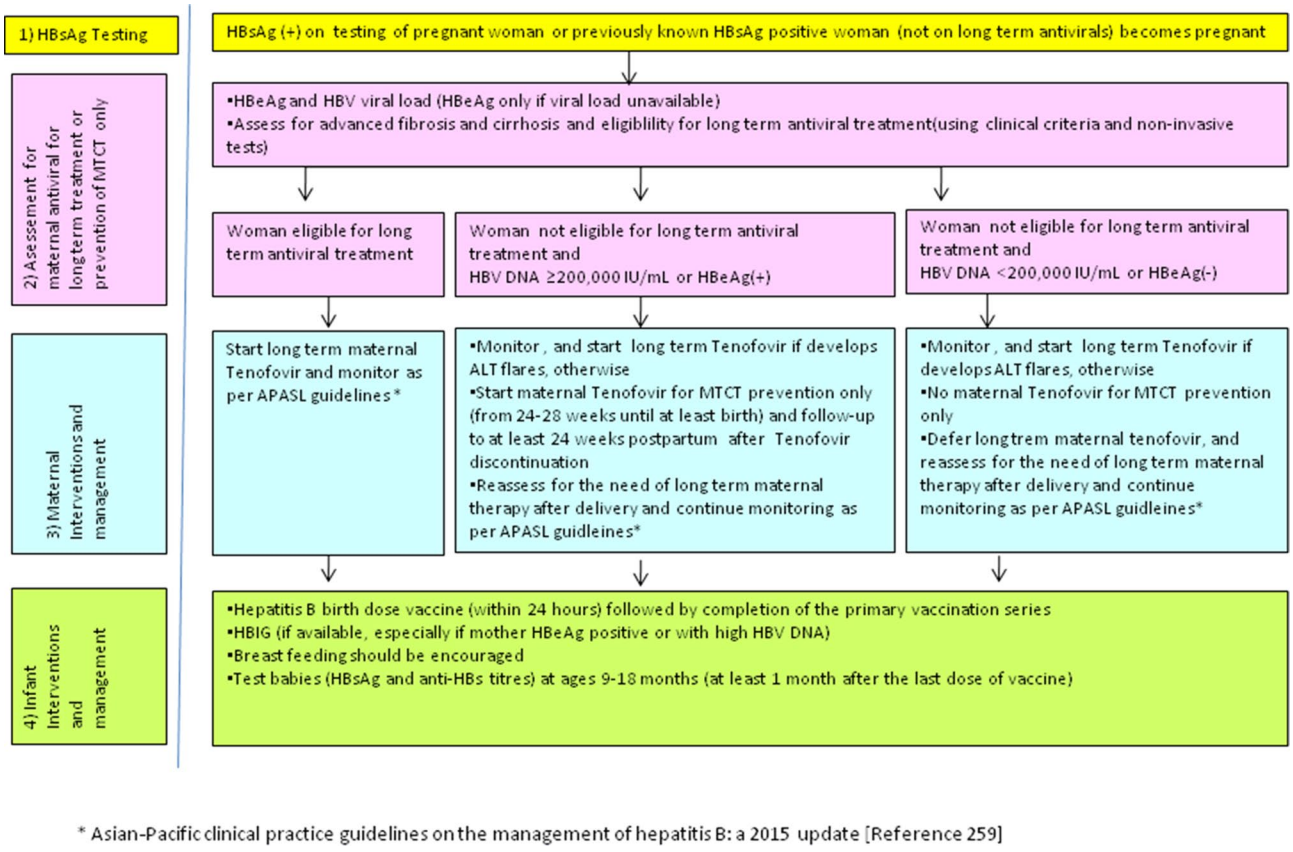

Fig. 1 Algorithm of maternal and infant management of pregnant females found to be HBsAg-positive first time during HBsAg screening during pregnancy or previously known chronic HBsAg-positive females who become pregnant (and are not on long-term antivirals)

of hepatitis B virus can be implemented using this as the base (Fig. 3) [231].

HBsAg screening of pregnant females

Universal HBsAg screening of pregnant females is being conducted in many regions and countries of the world, but is not done in resource-limited regions and countries [312]. Many countries have adopted routine screening of all pregnant females, regardless of the HBsAg seroprevalence in the general population [313]. Testing should be done as early as possible during pregnancy, so that appropriate measures can be undertaken for the management of the mother, and to reduce the risk of MTCT. If not done during pregnancy, screening can also be performed during labor or after delivery. Laboratory-based immunoassays are the preferred assays. In settings with limited access to laboratory testing and/or where access to rapid testing would facilitate linkage to care and treatment, rapid diagnostic tests (RDTs) can be used to improve access. According to WHO, in regions with ≥ 0.4% of HBsAg prevalence, further virological evaluation and staging of liver disease can be started after a single positive serological assay HBsAg detection. In regions with < 0.4% HBsAg prevalence, confirmation of HBsAg positivity on the same immunoassay with a neutralization step or a second different RDT assay should be considered [313].

The offering HBV testing alongside existing HIV services should be considered for scaling up HBV testing for pregnant females and their partners [231].

Pregnant females found to be HBsAg positive during screening should be tested HBV DNA or HBeAg or both, along with assessment of the severity of the liver disease. High levels of HBV DNA (≥ 200,000 IU/mL) and/or HBeAg positivity are associated with high risk of MTCT of HBV, and these females are candidates for antiviral therapy for prevention of MTCT. In an important meta-analysis, Ott et al. examined the global prevalence of HBeAg status in female of child-bearing age in 2005, and found a global prevalence of 24–32% which had only marginally decreased since 1990 [314]. Consequently, we can surmise that almost 1/3 of females of child-bearing age carry a higher risk of MTCT despite infant immunization and HBIG. In resource-limited settings, the WHO recommends HBeAg status to be tested as a surrogate marker for those with high viral load [see above].

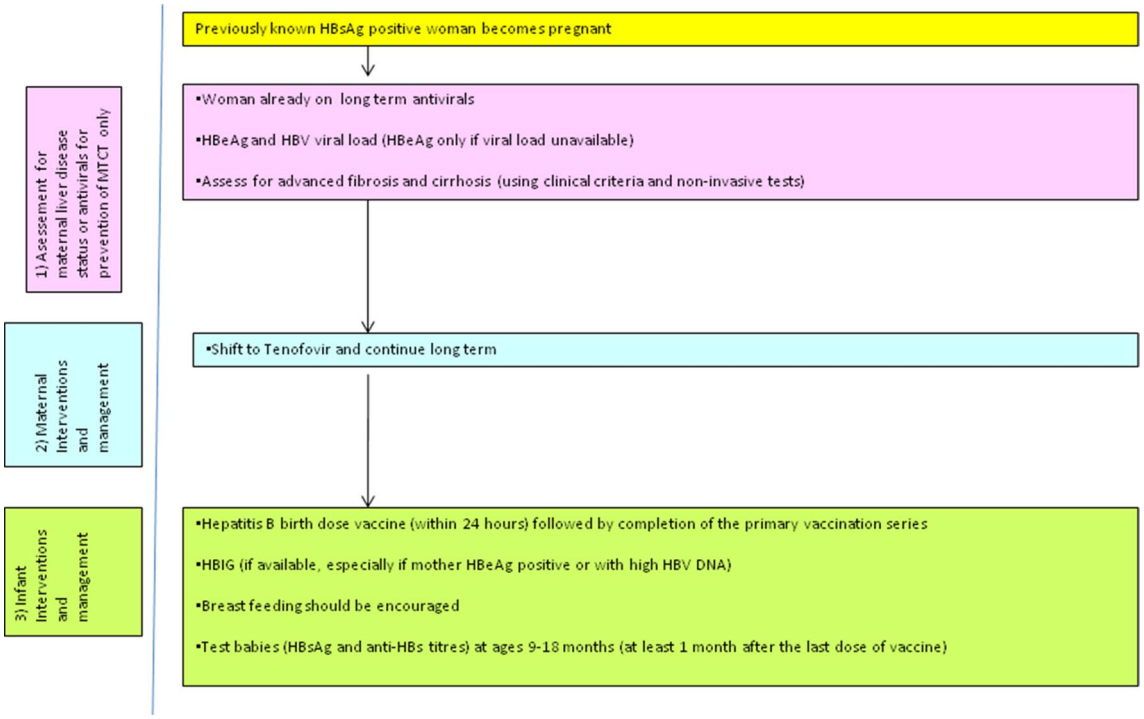

Fig. 2 Algorithm of maternal and infant management of previously known chronic HBsAg-positive females who become pregnant and are already on long-term antivirals

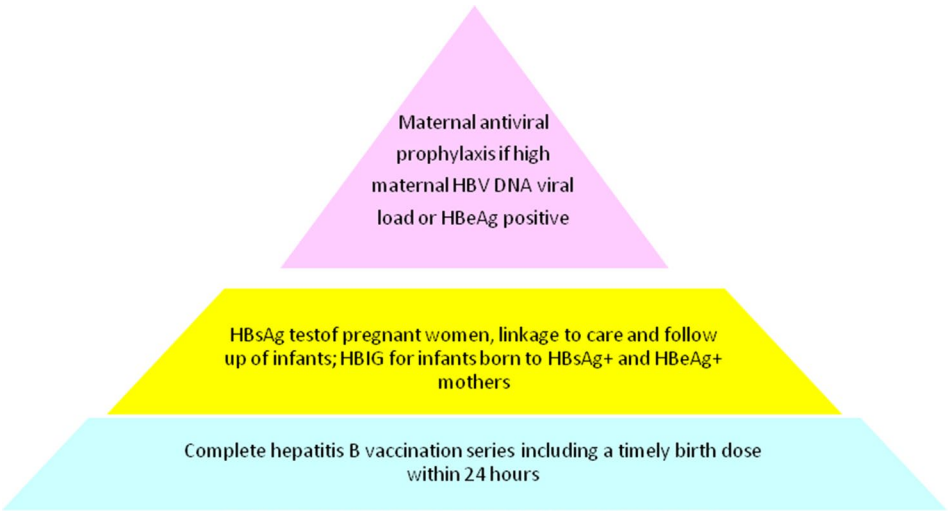

Fig. 3 Incremental epidemiological approaches to prevent mother-to-child transmission of hepatitis B virus infection

HBsAg screening of pregnant females should be accompanied by pre- and post-test counseling. Pre-test information should include: the benefits of early diagnosis of HBV infection for their own health, as well as to reduce the risk of MTCT; and importance of testing for other infections. Post-test information for HBsAg-positive females should include: use of antivirals for the mother if needed; measures to reduce the risk of MTCT of HBV infection; encouraging family and partner screening; encouraging to deliver in a health facility to ensure access to MTCT services; encouraging breastfeeding; and importance of HBsAg testing for the infant [313].

Linkage to care of the HBsAg-positive mother is also important, to prevent loss to follow up and missing the opportunity to assess liver disease in the mother and the need for antiviral treatment as appropriate. Unvaccinated HBsAg-negative pregnant females can be offered HBV vaccination. Follow-up of HBsAg-positive pregnant females should continue through the postpartum period and beyond as per the clinical situation [313].

A higher prevalence of HBV infection in the general population is found among pregnant females from marginalized or stigmatized groups (e.g., people who inject drugs, sex workers) or minority groups (migrants, indigenous populations). They also have poor access to health care. Integrated antenatal services for HBV, HIV, and syphilis provide an opportunity to reach out to marginalized and minority groups. Appropriate measures should be taken to ensure that these groups have access to health services without stigma and discrimination [231, 313].

Appropriate measures should be taken to maintain confidentiality and prevent stigma and discrimination against those females who are found to be HBsAg positive. Healthcare worker training and rights-based frameworks are needed to achieve this [231].

Prevention of mother-to-child transmission of hepatitis B virus

All infants should receive appropriate immunoprophylaxis as early as possible after birth [see above] [231].

Antivirals as an additional measure to prevent MTCT in selected pregnant females should be used [see above]. Epidemiological and modeling studies have suggested that infant HBV vaccination alone would be insufficient to reach the 0.1% HBsAg prevalence goal in children by 2030 [231]. Worldwide, scaling up HBV vaccination to a 90% coverage of the three-dose hepatitis B vaccine, including timely birth dose, would prevent an additional 14 million new neonatal HBV infections over the next 10 years. Giving tenofovir prophylaxis to eligible pregnant females in addition to the HBV vaccination (including timely birth dose) would prevent an additional 2.9–3.0 million neonatal infections over the same period [231]. HBeAg can be used as an alternative test in settings where access to HBV DNA quantification is limited [See above] [231]. The challenges in providing tenofovir prophylaxis for MTCT prevention in eligible pregnant females include costs and availability of HBV DNA tests and tenofovir, lack of trained health-care workers, and lack of capacity and infrastructure [231].

Use of tenofovir prophylaxis to prevent MTCT in addition to HBV vaccination can reduce health inequities in low-income regions where HBIG is not feasible. The drug is available within HIV national programs.

However, interventions based on testing of pregnant females followed by tenofovir prophylaxis are costlier than hepatitis B vaccination of infants alone. Therefore, tenofovir prophylaxis in addition to HBV vaccination may not be feasible in low-income regions currently [231].

Scaling up timely birth dose is the most cost-effective option. Countries that have not yet reached the 2020 goal of 1% HBsAg prevalence among under 5 children through vaccination should focus on increasing their vaccination coverage, including timely birth dose. Improving HepB-birth dose coverage is a first step as it is still < 90% in many countries of the Asia–Pacific (Table 2). Birth dose continues to be a challenge for countries with low rates of health facilities deliveries and lack of skilled birth attendants [315]. Community-based interventions can be enhanced by training village health volunteers and expanding HepB-BD in the community by giving birth dose in home in case of home deliveries, as reported from Myanmar. Vaccine out-of-the-cold chain is another option [316]. For countries with high rates of health facilities deliveries, providing the first dose of vaccine in delivery room should be considered.

In countries that have already scaled up the timely birth dose, adding antenatal HBsAg testing of pregnant females and tenofovir prophylaxis in eligible females is an additional measure to prevent MTCT which may be cost-effective in some regions [231]. All eligible pregnant and breastfeeding females living with HBV infection can safely use tenofovir [See above].

As reported in Table 2, the majority of countries in Asia–pacific have the capacity to provide HBsAg testing in ANC, but there are not yet effective national screening programs in routine for many of them. For positive HBsAg pregnant females, availability of HBV DNA and/or HBeAg testing is a concern for many countries. In these countries, ANC and deliveries are mainly conducted by midwives at the decentralized level (primary health centers, district hospitals) with no access to HBV DNA viral load measurement and immuno-enzymatic tests. The use of HBeAg rapid diagnosis tests as reported in Cambodia [255] or the use of HBV DNA point of care [317] could improve detection of pregnant females eligible for antivirals for MTCT prevention. Access to immunoglobulin is also limited in many countries of Asia–Pacific (Table 3).

Programmatic considerations

Strong government leadership, commitment, and multisectoral collaboration with a wide range of stakeholders are needed at all levels. Also, EMTCT of HBV activities must be integrated with the national/regional response to viral hepatitis. Normative guidance (including policies, guidelines, and implementation protocols) is needed for standardized implementation of services.

Civil society involvement in the planning, development, and implementation of the EMTCT programs should be encouraged.

Services delivery of HBV interventions for pregnant females should be guided by the principles of universal health coverage, so that a pregnant woman's ability to pay does not determine her access to available services. Efforts should be made to include HBV EMTCT services in national health insurance schemes to minimize out-of-pocket expenses.

Table 3 Current status of interventions to eliminate mother-to-child transmission (MTCT) of hepatitis B virus as public health policy in the different countries of Asia–Pacific

	Antenatal testing for HBsAg	Antenatal testing for HBeAg	HBV DNA if positive HBsAg	Antiviral prophylaxis for MTCT prevention (if yes, eligibility)	HBIG for exposed infants	Post-vaccination anti-HBs testing
North Asia						
Russia	Yes	Yes, partially	Limited. Out of pocket	Yes, if HBV DNA > 10^6 IU/ml	Yes, partially	No
Central Asia						
Afghanistan	No	NA	NA	NA	NA	NA
Kazakhstan	Yes	No	Yes	NA	NA	No
Kyrgyzstan	Yes, partially	No	Yes, partially	Yes, if HBV DNA > 10^7 IU/ml	NA	No
Tajikistan	Yes, partially	No	No	No	No	No
Turkmenistan	Yes, partially	No	No	No	No	No
Uzbekistan	Yes, partially	No	No	No	No	No
Western Asia						
Armenia	Yes	Yes, partially	Out of pocket	Out of pocket	Limited, out of pocket	No
Azerbaijan	Yes	No	No	No	No	No
Bahrain	Yes	No	No	Out of pocket	Out of pocket	No
Cyprus	Yes	No	No	Out of pocket	Out of pocket	No
Georgia	Yes	Yes, partially	Out of pocket	Out of pocket	Out of pocket	No
Iran	Yes, if high risk behavior	Yes, partially	Limited, out of pocket	Out of pocket	Yes	No
Iraq	NA	NA	NA	NA	NA	NA
Israel	Yes	Yes	Limited, out of pocket	Out of pocket	Yes	No
Jordan	Yes	No	Out of pocket	Out of pocket	Out of pocket	No
Kuwait	Yes	Yes, partially	Out of pocket	Out of pocket	Yes	No
Oman	Yes	Yes, partially	Out of pocket	Out of pocket	Yes	No
Qatar	Yes	Yes, partially	Out of pocket	Out of pocket	Yes	No
Saudi Arabia	Yes	Yes, partially	Out of pocket	Out of pocket	Out of pocket	No
Syria	NA	NA	NA	NA	NA	NA
Turkey	Yes	Yes	No	HBV DNA > 200,000 IU/mL or HBeAg +	Yes	Yes
United Arab Emirates	Yes	Yes	Out of pocket	Out of pocket	Yes	No
Yemen	NA	NA	NA	NA	NA	NA
East Asia						
China Mainland	Yes	Yes, partially	No	HBV DNA > 200,000 IU/mL	Yes	7–9 months, pilot only
Mongolia	Yes	Yes	Yes	HBeAg(+) with HBV DNA > 200,000 IU/mL	Yes, infants of HBeAg(+) mothers only	Yes, 2 months after completion of vaccination
South Korea (Republic of Korea)	Yes	Yes	Yes	HBV DNA > 200,000 IU/mL	Yes	Yes
North Korea (Democratic People's Republic of Korea)	NA	NA	NA	NA	NA	NA
Japan	Yes	Yes	Not official policy	Not official policy	Yes	Yes

Table 3 (continued)

	Antenatal testing for HBsAg	Antenatal testing for HBeAg	HBV DNA if positive HBsAg	Antiviral prophylaxis for MTCT prevention (if yes, eligibility)	HBIG for exposed infants	Post-vaccination anti-HBs testing
Taiwan	Yes	Yes	Yes	HBV DNA > 200,000 IU/mL	Yes	Yes
South-East Asia						
Brunei	Yes	Yes	Yes	HBV DNA > 10^6 IU/ml hepatology clinics	Yes	Yes, 9–12 months
Cambodia	Not in routine	Yes (RDT)	No	HBeAg algorithm in a research study	Limited. Out of pocket	No
Indonesia	Not in routine	No	No	No	Limited. Out of pocket	No
Lao PDR	Yes	No	No	No	Limited. Out of pocket	No
Malaysia	Yes	Yes	Yes	HBV DNA > 200,000 IU/mL or HBeAg +	Yes	Yes, 9 months
Myanmar	Not in routine	No	No	No	Limited. Out of pocket	No
Philippines	Yes	No	No	No	Limited. Out of pocket	No
Singapore	Yes	Yes	Yes	HBV DNA > 200,000 IU/mL	Yes	Yes, 3 months after completion of vaccination
Thailand	Yes	Yes	Yes	HBeAg + or HBV DNA > 200,000 IU/mL	Yes but out of pocket	Yes
Timor-Leste						
Vietnam	Yes	Yes	Yes	HBV DNA > 200,000 IU/mL	Yes	No
South Asia						
Bangladesh	Yes	Yes	Yes	Yes	Yes	No
Bhutan	NA	NA	NA	NA	NA	NA
India	Not as public health policy	Not as public health policy	Not as public health policy	Not as public health policy	Yes, but out of pocket	No
Maldives	NA	NA	NA	NA	NA	NA
Nepal	Yes	Yes	Yes	Yes	Yes	No
Pakistan	Yes	No	No	No	Yes	No
Sri Lanka	Not as public health policy	Not as public health policy	Not as public health policy	Not as public health policy	Not as public health policy	No
Pacific Countries						
Australia	Yes	Yes	Yes	HBV DNA > 200,000 IU/mL	Yes	Yes, 3–12 months after completing primary series
New Zealand	Yes	Yes	Yes	HBV DNA > 200,000 IU/mL	Yes	Yes, 3–12 months after completing primary series
American Samao	Yes	No	No	No	Yes	No
Cook Islands	Yes	No	No	No	Yes	No
Federated States of Micronesia	Yes	No	No	No	Yes	No
Fiji	Yes	No	No	No	Yes	No

Table 3 (continued)

	Antenatal testing for HBsAg	Antenatal testing for HBeAg	HBV DNA if positive HBsAg	Antiviral prophylaxis for MTCT prevention (if yes, eligibility)	HBIG for exposed infants	Post-vaccination anti-HBs testing
French Polynesia	Yes	No	No	No	Yes	No
Guam	Yes	No	No	No	Yes	No
Kiribati	Yes	Yes	Yes	NA	No	No
Marshall Islands	Yes	Yes	Yes	NA	No	No
Nauru	Yes	NA	NA	NA	No	No
New Caledonia	Yes	No	No	No	Yes	No
Niue	Yes	NA	NA	NA	NA	NA
Papua New Guinea	No	No	No	NA	No	No
Pitcairn	NA	NA	NA	NA	NA	NA
Samoa	Yes	NA	NA	NA	NA	NA
Solomon Islands	Yes	No	No	NA	No	No
Tokelau Islands	NA	NA	NA	NA	NA	NA
Tonga	Yes	NA	NA	NA	NA	NA
Tuvalu	NA	NA	NA	NA	NA	NA
Vanuatu	NA	NA	NA	NA	NA	NA
Wallis and Futuna Islands	NA	NA	NA	NA	NA	NA

HBV Hepatitis B virus, *HBsAg* Hepatitis B surface antigen, *HBeAg* Hepatitis B envelop antigen, *HBIG* Hepatitis B immunoglobulin

Stigma and discrimination may be experienced by peoples and families affected by hepatitis B. Confidentiality of test results must be ensured. Steps should be taken to prevent stigma and discrimination against HBsAg-positive pregnant females and other family members, in health-care settings and in the communities [231].

Training and capacity building of health workforce are needed to ensure availability of trained staff in providing EMTCT interventions. Training and capacity-building strategies related to EMTCT of HBV may include the development of algorithms for HBsAg screening of all pregnant females and appropriate measures to prevent MTCT (including timely administration of the HepB birth dose to all infants); training on assessment of liver diseases in the pregnant females and antivirals use for treatment of pregnant female or prevention of MTCT; training on follow-up of exposed infants, including post-vaccination serological testing; and follow-up of females with HBV infection after delivery.

Recommendations

All pregnant females should be screened for HBsAg as early as possible in the pregnancy. Screening should be performed in each pregnancy, regardless of previous HBV vaccination or previous negative HBsAg test results (C1).

HBsAg screening of pregnant females should include pre- and post-test counseling and linkage to further care as appropriate (C1).

Scaling up timely birth dose is the most cost-effective option for preventing MTCT. Countries that have not yet reached the 2020 goal of 1% HBsAg prevalence among under 5 children through vaccination should focus on increasing their vaccination coverage, including timely birth dose (A1).

Countries that have already scaled up the timely birth dose, adding antenatal HBsAg testing of pregnant females and tenofovir prophylaxis in eligible females as an additional opportunity to prevent MTCT may be cost-effective in some regions (B1).

Areas of future research

Studies to evaluate the efficacy of TDF in preventing MTCT of HBV among females whose infants did not receive HBIG or a timely birth dose are needed.

Different service delivery models for providing integrated HBV, HIV, and syphilis services to pregnant females need to be studied.

Evaluation of service delivery models and measures to provide equitable health services access without stigma and discrimination (especially to vulnerable, marginalized or minority groups) are required.

Conclusions

The purpose of these guidelines is to provide scientific and specific guidance for the management of chronic HBV-infected pregnant females and newborn from pregnancy planning to postpartum period. There are unavoidable limitations to the process of development of guidelines that mainly reflect the low quality of the existing clinical studies and the small number of good quality randomized controlled trials in pregnant females with chronic HBV infection.

There is a need for higher quality data and many potential areas of future research as highlighted after each section in these guidelines. Further scientific research in future will address many of the areas of uncertainty that currently exist. It is hoped that these guidelines will be used as guidance only and clinical judgment will be used by the practitioners in making clinical decisions for the benefit of their patients.

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Declarations

Conflict of interest Manoj Kumar, Zaigham Abbas, Milad Azami, Maria Belopolskaya, A. K. Dokmeci, Hasmik Ghazinyan, Jidong Jia, Ankur Jindal, Han Chu Lee, Wei Lei, Seng Gee Lim, Chun-Jen Liu, Qiang Li, Mamun Al Mahtab, David H. Muljono, Madunil Anuk Niriella, Masao Omata, Diana A. Payawal, Shiv K. Sarin, Olivier Ségéral, Tawesak Tanwandee, Nirupma Trehanpati, Kumar Visvanathan, Jin Mo Yang, Man-Fung Yuen, Yingjie Zheng, Y. H. Zhou declare that they have no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

Data availability All data, materials, and software applications support the published claims and comply with field standards.

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