

Pregnancy and Hepatitis B Immunization: A Commentary on Maternal Knowledge and Vertical Transmission Risks

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This commentary further expands on the topics touched on in the study “*Maternal knowledge of the risk of vertical transmission and offspring acquisition of hepatitis B*”. We discuss in detail hepatitis B in pregnancy, with a focus on screening, treatment and vaccination of new-borns. We also examine why the global coverage of hepatitis B vaccination at birth is astoundingly low, despite our knowledge of its efficacy. Then, we provide insight into the barriers to providing appropriate screening in the USA, as well as the importance of maternal education in the fight against hepatitis B, particularly with regards to mother to child transmission.

Hepatitis B in Pregnancy

The paper *Maternal knowledge of the risk of vertical transmission and offspring acquisition of hepatitis B*, recently published in *Annals of Hepatology* [1], provides unique insight on a topic not previously studied in the USA. The research paper discusses important topics on maternal hepatitis B infections.

Hepatitis B virus (HBV) infection remains a common infection with over 240 million people infected worldwide and up to 1.4 million people infected in the USA [2]. In the USA alone, up to 0.9% of pregnant women are infected with HBV. With >25,000 infants born to these women; vertical transmission is a considerable source of ongoing HBV infection. These rates however, vary by ethnicity and race with the highest rate seen in Asian women (6%), with lower impacts in Black (1%), White (0.6%) and Hispanic women (0.14%) [3].

Screening for chronic HBV during pregnancy has been recommended since 1998 and remains the current standard of care in the USA [3,4]. The current practice is to

screen all expecting mothers for hepatitis B surface antigen (HBsAg), antibodies to anti-hepatitis B surface antigen (anti-HBs) and anti-core total antibodies (anti-HBc) early in pregnancy. Those positive to HBsAg should have a full HBV serology, including hepatitis Be antigen (HBeAg), its antibody (anti-HBe) and HBV DNA [5]. Around 95% of pregnant women in the USA are being screened according to recent data [6].

Once identified as HBV positive via HBsAg testing, assessing the HBeAg and HBV DNA status of the mother further helps to determine the risk of transmission in the absence of immunoprophylaxis. Vertical transmission in HBeAg positive mothers can be as high as 70-90% [2]. However, the risk is significantly reduced with the administration of immunoprophylaxis to 5-10%.

The emphasis on prevention of vertical transmission is to reduce the burden of chronic HBV infection. Children who acquire HBV from vertical transmission have a 90% risk of becoming chronically infected, compared to <5-10% risk when older children or adults are infected. Infants of mothers HBeAg positive are more likely to remain chronically infected; 90% from HBeAg positive vs 40-70% from HBeAg negative mothers [3]. Children who acquired HBV from vertical transmission have higher viral loads and lower rates of seroconversion to negative HBeAg status. Though it is unusual to see development of cirrhosis during childhood in those with vertically acquired HBV, development of hepatocellular carcinoma (HCC) has been seen in children, even in those who had previously developed antibodies against HBeAg (anti-HBe). Given the high rates of chronic infection in cases of vertically acquired HBV and the subsequent liver disease, it is important to prevent vertical transmission [7].

The current strategy to minimize transmission is to use in combination the HBV vaccine with hepatitis B immunoglobulin (HBIG) at birth, and in some cases the use of antiviral therapy in the third trimester of pregnancy. Administering HBV vaccine and HBIG within the first 12 hours after birth has been shown to confer long term immunity in 85-95% of cases [3,8]. The efficacy of this combination is reduced when administration is delayed, particularly past 24 hours [9,10]. This practice is also recommended for infants born to mothers with an unknown HBV status at the time of delivery. Completion of the 3-part HBV vaccination series is recommended universally [2].

Although mother to child transmission (MTCT) of HBV more commonly occurs during the childbirth process, *in utero* transmission can occur in around 10% of infants, and is the likely cause of immunoprophylaxis failure [11]. This risk of transmission is largely linked to maternal viral load; however, invasive prenatal tests, particularly amniocentesis, can increase the risk of *in-utero* transmission [12,13]. Antiviral prophylaxis should be considered in pregnant women with high viral loads. Both, the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, recommend initiating maternal antiviral treatment with viral loads of >200,000 IU/mL [14,15]. Lamivudine, telbivudine, and tenofovir disoproxil fumarate (TDF) have been shown to be safe alternatives in pregnancy and decrease immunoprophylaxis failure in infants; TDF has demonstrated reduction in MTCT rates in HBeAg-positive mothers [16,17]. Antivirals are usually started in the third trimester of pregnancy, between 28-32 weeks, but preferably at 28 weeks, given the risk of suboptimal reduction of viral load in the event of pre-term birth. The antivirals are usually discontinued between birth and 3 months, depending on indication for continued antiviral therapy post-partum [14,15].

Breastfeeding is considered a safe practice in HBV positive mothers, with very low transmission risk, particularly when the infant has received appropriate immunoprophylaxis [2-4,9,18]. Breastfeeding can also be continued in mothers on antiviral therapy post-partum. Importantly, follow-up of both infant and mother must be continued to assess for immunoprophylaxis failure and to ensure the mother is receiving appropriate HBV management outside the perinatal period. Currently, it is recommended that infants be tested for HBsAg and anti-HBs at 9-12 months or 3 months after completion the HBV vaccination series. Re-vaccination is indicated in uninfected infants who did not develop antibodies, in order to minimize their horizontal risk of infection [19]. The above strategies have made a large dent in MTCT of HBV; however, increasing global vaccination rates is a key factor in the fight for eradication.

Why is Global Coverage of HBV Vaccine Low?

As mentioned in the original paper, only 38% of new-borns worldwide receive the birth dose of the hepatitis B vaccine. More recently, this percentage has marginally risen to 42% in 2018 [20]. Interestingly, despite the fact that vaccinating all infants for hepatitis B has proven to be extremely effective, there is still an impressive deficiency worldwide in ensuring this is done. So, what are the barriers to reaching a larger portion of the population for this vaccine? Factors contributing to the observed deficiency in vaccination are many, and can be divided into accessibility and resources, and education.

Accessibility and Resources

The absence of symptoms in many newly infected infants and new-borns contributes to the lack of appreciation for the burden of this disease on mothers. Unfortunately, new-borns are the group that is most susceptible to developing chronic HBV infection and ultimately cirrhosis [21]. Resource-related barriers have included lack of financial support, insufficient cold chain storage and a lack of skilled birth attendants or trained healthcare workers available during or after the birth [22].

Securing funding for vaccination services in many countries continues to be a challenge. Currently, in many low-income countries, less than 40% of needs for vaccines and routine immunizations are financed by the governments, while others remain completely reliant on donor funding [23]. This places many countries in a vulnerable position, where financing could be affected by changes in donor priorities [24]. Efforts are being made on a global level to address these issues and provide particular countries a more stable funding source to cover the costs of vaccines. One such organization is the Global Alliance for Vaccines and Immunizations (GAVI), which combines the efforts and resources of the World Health Organization (WHO), United Nations International Children's Fund (UNICEF), the World Bank, and both sovereign governments and private foundations to provide a steady and sustained source of funding [24]. While funding for vaccination remains an issue that is being tackled on a global level; the economic barrier is also very present on a personal level. In one study assessing the hepatitis B vaccination patterns among healthcare workers (HCW) in 11 countries in Africa, cost was reported as the biggest barrier to vaccination [25]. Similarly, in a study in Ghana, 62% of participants reported cost as being their barrier to vaccination [26]. Unfortunately, these findings are not specific to hepatitis B vaccination; cost has been a barrier to many other vaccination programs in low-income countries.

Vaccine instability and cold chain storage is another barrier in low-income countries. Fortunately, data has demonstrated that the monovalent hepatitis B vaccine is thermostable for at least 4 weeks at temperatures between 37°C and 40°–45°C and provides a similar level of protection and seroconversion [22]. This would allow countries, particularly in the African region and the Amazon region, where cold chain storage is less uniformly available, to overcome this particular barrier in providing timely vaccinations. Controlled temperature chain is a newer approach to the storage and transportation of vaccinations, one in which they are allowed to be kept outside of the traditional cold chain for a short period of time. This approach has demonstrated tremendous benefits in cost-saving and in reducing the burden of perinatal HBV infection [27].

Many countries with low vaccination rates continue to have high rates of home births, hindering accessibility to routine post-natal care for mother and infant, including vaccinations. In one study performed in Laos, providing HCW and village health volunteers with the means to perform outreach during post-natal care, led to a significant improvement in hepatitis B vaccine birth dose administration [28]. Unfortunately, another study demonstrated that despite many centers provided postnatal home visits, not all were able to administer a hepatitis B birth dose vaccine due to supply issues [29]. This finding brings us back to cost and resources being a key factor in the low rates of vaccination in low-income countries, independent of location of birth and access to HCW.

In the United States, chronic HBV is more likely to affect vulnerable populations and minorities. Studies have demonstrated that Asian Americans, Pacific Islanders, and Blacks—particularly foreign-born Blacks—have higher rates of hepatitis B infections [30,31]. In addition, Asian and Pacific Islanders have the highest incidence rate of HCC and HCC-related mortality [32]. These data do not specifically pertain to the pregnant patient population; however, pregnant females that belong to these communities fall into this category where there is an increased likelihood that testing may not be provided per the current guidelines. As mentioned previously, 95% of women are currently being screened appropriately. However, in order to meet the goals of eradicating MTCT in the USA, 100% of women should be screened.

Accessibility and cost play an important role in prenatal care and screening. Currently, women without health insurance who become pregnant can apply for social health insurance or Children's Health Insurance Program (CHIP) depending on their income, household size, citizenship and immigration status [33]. Although these

are excellent options for many women around the country, certain eligibility requirements may preclude women from obtaining affordable coverage and therefore will prevent them from seeking care and receiving appropriate prenatal testing altogether.

Education

Education is an important step in reaching most of the population, and needs to occur at multiple levels. When looking into barriers to appropriate HBV screening, knowledge gaps in the general population and in medical professionals, education plays a large role. One study surveying Chinese immigrants in North America on their knowledge and beliefs about hepatitis demonstrated that a proportion of Chinese immigrants believes a stress-free mind, adequate sleep, and certain herbal teas could be used as “precautionary measures” against the infection. This same study reported that some interviewees stated they would be reluctant to be tested at all, citing reasons such as associating hospitals with bad luck. Up to 30% of people in the Asian American community believed general check-ups or vaccination is not necessary [34,35]. When questioned about their knowledge about HBV vaccines, many interviewees live with the misconception that vaccines should be given after someone has been diagnosed with hepatitis B, only to prevent further worsening of the disease [34]. Although these surveys were administered to the general population, it may be a fair assumption that pregnant females not educated on HBV screening, therapy and immunization may not get the appropriate care if their healthcare provider does not routinely educate and screen their pregnant patients.

Interestingly, a study looking to investigate physicians' knowledge regarding chronic HBV diagnosis, screening, and management demonstrated that there were fundamental knowledge gaps relating to all parts of the survey. Most notably, only 24% of participants identified the correct screening test [36]. Given that HBsAg testing is part of the American College of Obstetrics and Gynaecology guidelines in prenatal care, one could assume that with regards to obstetricians, knowledge gaps are less likely to contribute to this issue [37]. One study looking at peripartum care practices of obstetricians and midwives at a major health system in the USA, demonstrated that 97% reported consistent testing for hepatitis B; however, only 91% selected the correct screening test [38]. Another study surveying Obstetrics and Gynaecology program directors and residents around the USA demonstrated that all the program directors that participated and 95.2% of residents reported screening for hepatitis B at the first prenatal visit. This study also demonstrated that although screening rates were high, only 19.6% of program directors and 12.6% of residents knew that third-trimester antiviral therapy is

recommended for women with viral loads >200,000 IU/mL [39]. The above two studies demonstrate how critical Continuing Medical Education is.

As mentioned in the original paper, mothers of 5-15.5% of children lacked essential knowledge relating to HBV prevention and diagnosis in the perinatal setting. Data on maternal understanding of the disease and the role of screening, treatment and vaccination is somewhat limited, particularly in the USA.

One study in Vietnam assessing the knowledge and attitudes of pregnant women surrounding HBV prevention and immunization demonstrated a marked deficiency in knowledge regarding the disease, with only 10.8% of participants correctly answering all questions about HBV transmission, routes and preventive measures. It also reported that only 66% of participants stated they would be willing to have their child vaccinated 24 hours post-birth. They did demonstrate that receiving information about HBV during pregnancy was significantly associated with better HBV knowledge scores [40]. A similar study in Cameroon also demonstrated poor knowledge in pregnant women with regards to HBV, highlighting the importance of providing education, particularly during prenatal visits [41]. In Japan, a randomized controlled trial that assigned pregnant parents to receive education sessions pertaining to childhood vaccinations or no education, demonstrated that providing education to both parents, and also individually to the mother, was an effective way to improve immunization rates [42]. This study was not specific to hepatitis B, but discussed all recommended childhood vaccines.

An educational tool entitled *Hepatitis B and You* was developed in the late 1990s and was later adopted by the CDC. Slides from this book were published in the CDC website in 2000. The information in the book and its slides aimed at providing information about hepatitis B to patients at a sixth-grade level and to encourage them to become active participants in their care. A survey taken by the participants reported that 86% of respondents believed their knowledge about hepatitis B improved after reading the slide set [43].

Multiple studies have demonstrated the importance of targeting parental knowledge on childhood vaccinations and its effect on vaccine coverage. In a study aiming to improve hepatitis B birth dose vaccination rates, the authors identified knowledge gaps by both the parents and health providers as barriers to vaccination. A standardized approach to the education of providers and parents was taken. Parent education was provided in the form of educational materials, resources to institutional web pages, and the involvement of non-medical care team members, such as religious liaisons, as part of the education process.

Vaccination rates by 12 hours of life increased from 21.5% to 42.5%, and vaccination rates by hospital discharge increased from 52.4% to 72.5% [44].

There has been an increase in the rate of young adults unwilling to receive vaccinations, with one study demonstrating that up to 30% of them cite safety concerns, particularly the fear of vaccines leading to autism, as the greatest barrier. [45] With the uptick in vaccine hesitancy among patients in North America in particular, the PromoVac study, performed in Canada, was aimed at evaluating the effect of motivational interviewing on new parents' willingness to vaccinate their children. The study was performed to educate parents on all childhood vaccines and did demonstrate an improvement in vaccine coverage rates when motivational interviewing techniques were used [46]. Similarly, a randomized controlled trial comparing the effect of video and written education material on parents with vaccine hesitancy found that they were able to significantly reduce vaccine hesitancy by means of education alone [47].

Knowledge gaps lead to vaccination hesitancy and play a substantial role in the lower rates of hepatitis B vaccination. Multiple studies have demonstrated the importance that maternal education plays on vaccination rates and willingness to vaccinate their children. It allows mothers to take a more active role in her and her baby's health and may improve immunization rates overall.

Conclusion

There has been significant progress made in the fight to eradicate chronic hepatitis B.

However, until we are able to generate systems for equal access to health care; create educational health programs for health promotion; and promote widespread screening, treatment, and vaccination rates, there will always be a significant problem for the at-risk population.

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