

UDC 616.36-002-053.31-07(479.25)

DOI:10.54503/0514-7484-2022-62.4-114

Impact of HBsAg Serological Testing in Pregnant Women for Improvement of Hepatitis B Vaccinations in Newborns in Armenia

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Key words: HBsAg serological testing, hepatitis B virus, morbidity, pregnant women, vaccination.

Introduction

Hepatitis B is a life-threatening infection caused by the hepatitis B virus (HBV). It is a major problem for health care systems worldwide due to causing chronic infection which can lead to liver cirrhosis and hepatocellular carcinoma (HCC) [19]. In 2015, the prevalence of HBV infection among general population globally was estimated at 3.5% with nearly 257 million people living with chronic hepatitis B (CHB) [8]. It is estimated that around 650,000 people worldwide die each year from the complications of CHB [9, 21]. Hepatitis B surface antigen (HBsAg) is a surface protein of HBV that has an epidemiological significance as detection of its high levels in the serum is an indication of acute or chronic infection and that the individual is infectious [2,4,6,7]. Hepatitis B e-antigen (HBeAg) is a small polypeptide that exists in the serum during early phase of hepatitis B infection, soon after the HBsAg becomes detectable. Infants born to mothers who tested positive for both HBsAg and hepatitis B e-antigen (HBeAg) are at a higher risk of developing the infection (transmission risk 70%–90%), whereas those born to mothers positive only for the HBsAg bear a lower transmission risk of 5%–30% [10,13]. In addition, up to 90% of those perinatal cases become chronic infections [12, 18].

The Advisory Committee on Immunization Practices (ACIP) recommends immunoprophylaxis (using hepatitis B (HepB) vaccine and hepatitis B immune globulin (HBIG)) for infants born to HBsAg positive women within 12 hours of birth, followed by completion of HepB vaccine series and post-vaccination serological testing for vaccine induced antibody and HBV infection [4, 16]. When used alone, HepB vaccine is effective only in preventing perinatal HBV transmission by 71-75%, whereas the combined efficacy of HepB vaccine

and HBIG usage is higher (up to 94%), including for infants born to HBsAg positive women [1, 5, 16].

Timely birth dose vaccination (within 24 hours after birth) against HBV is a key intervention for preventing the transmission of the virus from mother to infant at birth, which could be enhanced by antenatal testing [19, 20].

In Armenia, hepatitis B vaccine has been offered to children since 1999. It is currently administered to appropriate target group of children according to the national schedule of immunization, that is through 4-dose schedule: hepatitis B vaccine monovalent birth dose followed by three doses of combination of vaccines for diphtheria, tetanus, pertussis, hepatitis B virus, Haemophilus influenzae b, poliomyelitis (DTP-HBV-HIB-IPV) [14].

The aim of this study was to assess the effectiveness of HBsAg serological testing offered to pregnant women in order to improve the HepB vaccinations in infants in Armenia.

Material and Methods

HBsAg serological testing of pregnant women

The retrospective cohort study included information from a pilot program conducted between July 2010 and July 2013, as a part of which a new epidemiological surveillance system was introduced to report and monitor HBV infections in pregnant women, (including HBsAg serological testing of pregnant women) in seven antenatal clinics in Yerevan, Armenia. In all clinics involved in the pilot program at the time, the HBsAg serological testing was offered to pregnant women as a part of antenatal care. We studied the impact of the HBsAg serological testing on the HepB birth dose vaccinations in newborns in Armenia from 2008 to 2015.

Coverage of hepatitis B vaccination in infants

The coverage of the total birth dose and timely birth dose of the hepatitis B vaccination (within 24 hours of birth) in newborns both in Yerevan and in other regions (provinces) of Armenia was calculated by the following ratios:

$$ov = \frac{(V_{total} \cdot 100)}{P}, \quad ov = \frac{(V_{timely} \cdot 100)}{P},$$
 Cov- is the coverage of the hepatitis B vaccination, V_{total} – is the number of total vaccinated newborns, V_{timely} – is the number of timely vaccinated newborns, P-is the number of appropriate target group of newborns.

Information of 12,9621 newborns in Yerevan and 19,5173 newborns in other provinces of Armenia was analysed.

Statistical analysis

The median (Me) age of pregnant women infected with HBV, mean (M) of cases of HBV infections in pregnant women, and standard deviation (SD) by years were calculated. The prevalence of hepatitis B in pregnant women in Yerevan was determined using the 95% confidence interval (CI) method.

To assess the effectiveness of HBsAg serological testing offered to pregnant women, data were analyzed using Chi square test (χ^2). The total number of vaccinated infants and the number of timely vaccinated infants during 2008-2010 and 2010-2013 were compared using actual and predicted numbers, p-values less than 0.05 were considered statistically significant.

We also studied the prevalence of HBV infection (between 2008 and 2018) and HBV carrier state (between 2016 and 2018) in general population and among women per 100 000 of people in Armenia. Morbidity rates (MR) was calculated by the following ratio: $MR = \frac{n}{P} \times 100\,000$, n- is the number of cases of HBV infection, or number of carriers of HBV, P- is the number of total population, or number of women in Armenia

We used the database of the National Centre for Disease Control (NCDCP) of Armenia

Results and Discussion

The prevalence of HBV infection in pregnant women in Yerevan

We investigated the retrospective data of the cohort of 6,789 pregnant women that were tested for HBsAg during 2010-2013. 70 (1.03%) out of 6789 women (M=17,5), (95% CI 15-20) were HBsAg positive. The prevalence of the cases of HBV infection in pregnant women by years in Yerevan during 2010-2013 were as follows: 2010: n=14, M=2,3 (95% CI 1,51-3,09); 2011: n=33, M=2,75 (95% CI 2,19-3,31); 2012: n=10, M=0,85 (95% CI 0,092-1,57); 2013: n=13, M=1,86 (95% CI 0,5-3,22) in 2013 (Table 1).

Table 1

The HBsAg positive cases among pregnant women in Yerevan

Year	Examined pregnant women	HBsAg positive cases(n)	M \pm SD	95% CI
2010	1035	14	2,3 \pm 1.5	1,51 – 3,09
2011	2486	33	2,75 \pm 1.65	2,19 – 3,31
2012	1928	10	0,85 \pm 1.19	0,092 – 1,57
2013	1340	13	1,86 \pm 2.5	0,5 – 3,32
Total	6789	70	17,5 \pm 10.5	15 – 20

Dynamics of the total and timely coverage indicators at birth dose of the hepatitis B vaccine in newborns

In the study, the retrospective data of coverage indicators of total and timely birth dose of the hepatitis B vaccine among newborns in Yerevan and in other provinces of Armenia were analyzed for the period between 2008 and 2015.

In provinces of Armenia, in 2008, the number of total and timely vaccinated newborns was 25,764 and 23,579 respectively; in 2009: 26,927 and 25,107; in 2010: 26,336 and 25,785; in 2011: 25,219 and 25,144; in 2012: 25,640 and 25,539; in 2013: 20,285 and 20,285; in 2014: 20,280 and 19,480 and in 2015: 18,676 and 18,039.

In Yerevan, in 2008, the number of total and timely vaccinated newborns was 12,342 and 10,936 respectively; in 2009: 13,163 and 12,096; in 2010: 12,683 and 12,435; in 2011: 13,100 and 13,085; in 2012: 12,519 and 12,513; in 2013: 16,265 and 15,327; in 2014: 20,571 and 18,526; in 2015: 20,388 and 19,384.

Our analysis showed that in Yerevan, the coverage indicator of total birth dose of the hepatitis B vaccine decreased between 2009 and 2010 (from 99% to 95%), but increased between 2010 and 2012, (from 95% to 100%), it decreased again in 2013 (to 83%), then increased again in 2014 and in 2015 (92% and 91%) (Fig. 2).

In provinces of Armenia the coverage indicator of total birth dose of the hepatitis B vaccine decreased between 2009 and 2012 (from 99% to 93%), it increased in 2013 (100%), then again decreased in 2014 and in 2015 (97%) (Fig. 1).

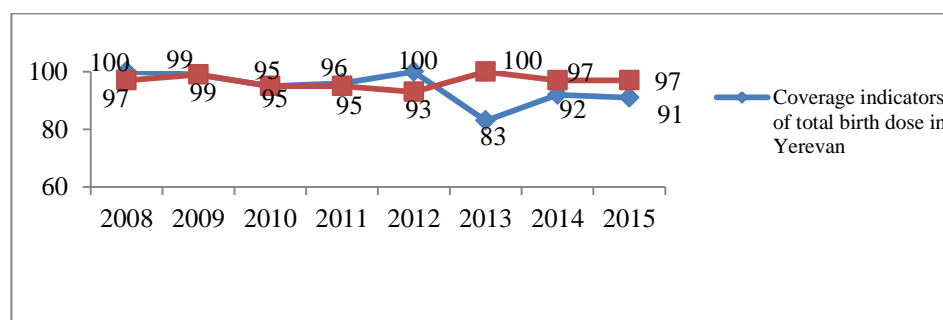


Fig. 1. Total coverage indicators (%) of birth dose of the hepatitis B vaccine in newborns in Yerevan and provinces of Armenia.

In Yerevan the coverage indicator of timely birth dose of the hepatitis B vaccine increased between 2008 and 2012 (from 89% to 100%); then decreased in 2013 (80%), then increased again in 2014 and 2015 (83% and 86%) (Fig. 2).

Whereas in provinces of Armenia, the coverage indicator of total birth dose of the hepatitis B vaccine increased between 2008 and 2010 (from 88% to 94%), decreased in 2011 and 2012 (93% and 92%), it increased in 2013 (100%), and then again decreased in 2014 and 2015 (94%) (Fig. 2).

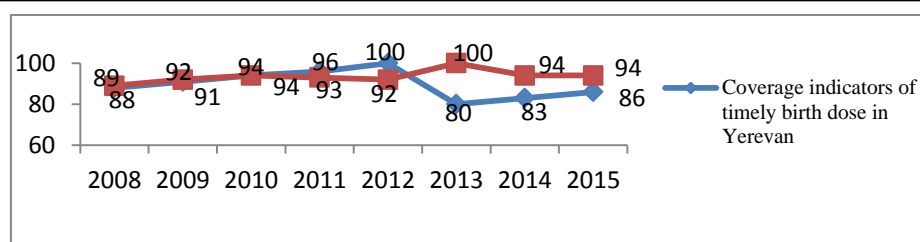


Fig. 2. Timely coverage indicators (%) of birth dose of the hepatitis B vaccine in newborns in Yerevan and provinces of Armenia.

Effectiveness of HBsAg serological testing of pregnant women on hepatitis B vaccination in newborns

A Chi-Square Test was used to determine the statistical significance of the effectiveness of the HBsAg serological testing offered to pregnant women as a part of antenatal care to improve vaccinations of birth dose of HepB vaccine in Yerevan. We compared the number of total vaccinated infants with the number of timely vaccinated infants during 2008-2010 and 2010-2013 in Yerevan (Table 2).

Table 2
The number of total and timely vaccinated newborns to hepatitis B in Yerevan 2008-2010 and 2011-2013

Years	Total vaccinated	Timely vaccinated	χ^2	p
2008-2010	38319	35467	29,9	<0,001
2011-2013	41884	40925		

Data analysis showed statistical significance of increase of the number of timely vaccinated newborns as a result of pregnant women being offered a HBsAg serological testing during 2010-2013 in Yerevan ($p < 0.001$).

The incidences of HBV infection and carriers of HBV among the general population and women in Armenia

The incidences of HBV infection (2008-2018) and carriers of HBV (2016-2018) in general population in Armenia were studied.

The cases of HBV infection included acute and initial diagnosis of chronic HBV. Of the 772 total cases, 276 (36%) were women.

Between 2016 and 2018, a total of 1,460 cases of carriers of HBV were recorded, of which 697 (48%) were women. We observed that the rates of carriers of HBV increased from 10.8 to 21.7 and from 9.9 to 19.4 (per 100,000 people) respectively during 2016-2018 in total general population and in women, in both cases, HBV carriers' rate have doubled (Fig. 3).

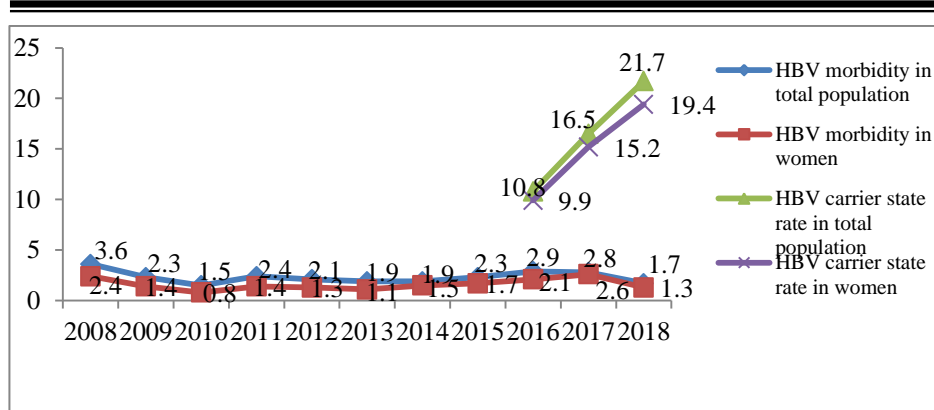


Fig. 3. The incidences of HBV infection (2008-2018) and carriers of HBV (2016-2018) among the total population and in women in Armenia (per 100,000 people).

Our data indicate 1.03% prevalence of HBV infection among pregnant women in Yerevan ($n=70$, $M \pm SD = 17.5 \pm 10.5$, 95% CI 15-20) demonstrated by the data analysis of the HBsAg serological testing of pregnant women in antenatal clinics conducted in Yerevan from July 2010 to July 2013.

In this study, we also provided insights into prevalence of HBV infections in Armenia among the total population and among women between 2008 and 2018 to demonstrate burden and importance of prevention of HBV infection.

We observed high incidences of HBV infection and its carrier rates among the total population and among women in Armenia. Although universal vaccination has reduced the incidence of HBV infection between 2008 and 2018, cases are still common (Fig. 3). An alarming finding was the significant increase of HBV carriers rate during 2016-2018; from 10.8 to 21.7 among the total population and from 9.9 to 19.4 among women, 48% ($n=697$) out of HBV carriers ($n=1,460$) were women.

The similar findings were presented in the previous studies. *Of the 134 women, HBsAg screening test positive results was 4.5% (95% CI 0.99%–8.01%)* in South Africa in 2014 [3]. Of the 3,238 women enrolled, 7.4% ($n=241$, 95% CI 6.6% to 8.4%) were HBsAg positive in Nigeria in 2017 [11]. In Spain, HBsAg prevalence in pregnant women was 0.42% (95% CI 0.33-0.50) in 2015 [15].

HBsAg prevalence among general population and among pregnant women were estimated in Italy and in Greece between 2005 and 2015. In Italy, HBsAg prevalence in general population was 0.8% (95% CI 0.4-1.0), in pregnant women was 0.8% (95% CI 0.7-1.0). In Greece, in general population was 3.3% (95% CI 2.2-4.7), in pregnant women was 2.9% (95% CI 2.4-3.5) [17].

It was previously described that timely birth dose (within 24 hours after birth) of the hepatitis B vaccine is important factor for prevention of hepatitis B infection from mother to infant at birth [19,20]. In order to assess the effectiveness of HBsAg serological testing offered to pregnant women for improvement of hepatitis B vaccinations in newborns in Armenia, we studied dynamics of total and timely coverage indicators in birth dose of the hepatitis B vaccine of infants in Yerevan and in provinces of Armenia during 2008-2015 (during HBsAg testing, before and after) to compare the rates of birth dose vaccinations. As HBsAg testing among pregnant women conducted only in Yerevan, we showed that the coverage indicator of total and timely birth dose of the hepatitis B vaccine increased on the whole during 2010-2013 in Yerevan, in comparison with provinces (Fig. 1, Fig. 2).

Epidemiological surveillance of HBV infections in pregnant women, including reporting and monitoring of cases was improved in Yerevan during 2010-2013. It provided much useful information of HBV infections in pregnant women and measures undertaken by the antenatal clinics for prevention of mother to child transmission. These measures contributed to the improvement of the total and timely infants' vaccinations for hepatitis B in maternity clinics in Yerevan ($p < 0.001$).

The improvement of vaccinations against hepatitis B in Yerevan was largely related to the introduction of epidemiological surveillance system of HBV infections, HBsAg serological testing of pregnant women and appropriate reporting, and monitoring in antenatal clinics.

There is an urgent need to implement effective prevention strategies to lessen the HBV burden among pregnant women and to prevent HBV infection in infants.

Conclusions

The results of our study suggest recommendations to improve epidemiological surveillance system of hepatitis B among pregnant women in Armenia, including HBsAg serological testing of pregnant women in the last trimester of pregnancy, recording, reporting and monitoring of cases of hepatitis B infections due to the importance of timely vaccinations of infants by HepB vaccine and combined efficacy using of the HepB vaccine and HBIG for immunoprophylaxis of hepatitis B in infants born to HBsAg positive women. It is also vital to conduct awareness campaigns among pregnant women to educate them the importance of serological testing (for prevention of mother to child transmission) and vaccination against HBV in antenatal clinics. These measures will enable to better assess the prevalence of HBV infection in pregnant women nationally and will improve the hepatitis B vaccinations in newborns.

Conflicts of Interest:

The authors declared no potential conflicts of interest with respect to the research, authorship and publication of this article.

Acknowledgment:

We thank the National Center for Disease Control and Prevention of Ministry of Health of RA for provision of data.

Accepted 07.07.22

Влияние серологического тестирования беременных на HBsAg для улучшения вакцинации новорожденных против гепатита В в Армении

Н.С.Мелконян, А.С.Оганесян, А.Р.Бадалян

Результаты проведенного исследования массового серологического тестирования на носительство HBsAg вирусного гепатита среди 6789 беременных женщин, за период с июля 2010г. по июль 2013г., выявили наличие HBsAg в 1,03% ($n=70$, $M\pm SD=17,5\pm 10,5$, 95% CI 15–20).

Полная и своевременная вакцинация новорожденных первой дозой вакцины против гепатита В в г.Ереване за 2010-2013гг. достоверно улучшилась ($p<0,001$). Распространенность гепатита В среди всего населения и среди женщин в Армении за 2016-2018 гг. все еще продолжается. Показатели носительства гепатита В среди всего населения увеличились с 10,8 до 21,7, а среди женщин – с 9,9 до 19,4.

Հայաստանում հղիների HBsAg-ի շճաբանական թեստավորման ազդեցությունը նորածինների հեպատիտ Բ-ի պատվաստումների բարելավման համար

Ն.Ս. Մելքոնյան, Հ.Ս. Հովհաննիսյան, Ա.Ռ. Բադալյան

Հետազոտության արդյունքները վկայում են, որ Երևանում 2010-2013թթ. ընթացքում 6789 հղիների զանգվածային սքրինինգի արդյունքում HBsAg-վիրուսակրության տարածվածությունը կազմել է 1,03% ($n=70$, $M\pm SD=17,5\pm 10,5$, 95% CI 15–20): Երևանում նորածինների շրջանում կատարված հեպատիտ Բ-ի ընդհանուր և ժամանակին պատվաստումները բարելավվել են 2010-2013թթ. ընթացքում, որը սերտորեն կապված է հղիների զանգվածային սքրինինգի հետ ($p<0,001$): Հեպատիտ Բ-ի տարածվածությունը դեռևս շարունակվում է ազգաբնակչության և կանանց շրջանում, 2016-2018թթ. բնակչության շրջանում հեպատիտ Բ-ի վիրուսակրության ցուցանիշն ավելացել է 10,8-ից մինչև 21,7, իսկ կանանց շրջանում՝ 9,9-ից մինչև 19,4:

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