

DETECTION OF HEPATITIS B SURFACE ANTIGEN IN PREGNANT WOMEN ATTENDING A PUBLIC HOSPITAL FOR DELIVERY: IMPLICATION FOR VACCINATION STRATEGY IN BANGLADESH

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Abstract. Routine antenatal hepatitis B surface antigen (HBsAg) screening and immunization of risk babies is very effective in preventing perinatal transmission of hepatitis B virus (HBV). We studied 1,800 parturients attending a public hospital to assess the rationale for such vaccination in Bangladesh. In one in every 29 deliveries (63 of 1,800 or 3.5%), the mother was found to be HBsAg positive. All were asymptomatic and many (41 of 63 or 65%) without risk factors would remain undetected if HBsAg screening were performed on selected groups. Most of the HBsAg-positive mothers (54 of 63 or 85.7%) were found to be chronic carriers and 30.2% (19 of 63) were also hepatitis B e antigen (HBeAg) positive, indicating high infectivity. Although 23 cord blood were positive for HBsAg or HBeAg, none were positive for IgM antibody to hepatitis B core antigen (IgM anti-HBc), suggesting transplacental transmission of the antigens rather than intrauterine infection. These findings are discussed in relation to the cost-effectiveness of routine prenatal screening and immunization of risk babies compared with universal infant immunization.

Perinatal transmission of hepatitis B virus (HBV) from infected mother to infant often leads to severe long-term sequel. Infants born to mothers positive for both hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) have a 70–90% chance of acquiring perinatal HBV infection, and 85–90% of infected infants become chronic carriers.^{1–2} These carrier children have an approximate lifetime risk of 25% of dying of primary hepatocellular carcinoma or cirrhosis,^{3–5} and the deaths usually occur during adulthood when familial and financial responsibilities are maximum. In addition, since most neonatal infections are asymptomatic or clinically mild, they serve as a source of HBV infection in their families and communities. Many become carrier mothers themselves and perpetuate the cycle.⁶ Prevention of perinatal transmission is possible with immunoprophylaxis of risk babies shortly after birth.^{2, 7–10} Prenatal HBsAg screening would identify infected mothers and thus allow immunization of their newborns with hepatitis B immune globulin (HBIG) and hepatitis B vaccine, a regimen that is 85–95% effective in preventing development of chronic HBV carrier state.^{2, 9–11} However, to obtain a complete control over the disease, the population at risk of acquiring the infection from other than perinatal transmission should also be immunized. The Global Advisory Group of the Expanded Program on Immunization has recommended and World Health Assembly has endorsed that the countries with more than 2% prevalence of HBV carriers should add hepatitis B vaccine in their routine infant immunization schedules.¹² In the South-east Asian region, only Indonesia, Mongolia, Thailand, and the Maldives have begun routine hepatitis B immunization, but this has not been possible in other countries due to economic reasons. However, the cost-effectiveness of maternal HBsAg screening and vaccination of risk babies in the context of health care service in Bangladesh have never been studied. Little information is available regarding the prevalence of hepatitis B infection and no data are available regarding hepatitis B infection among pregnant women in Bangladesh. In addition, persons providing health care to pregnant women often are not aware of the risks of perinatal

transmission of HBV infection. Routine HBsAg screening of all pregnant women may be initiated as part of regular antenatal checkup where the facilities are available. However, selective passive-active immunization also requires a supply of HBIG. This study was carried out to estimate the economic rationale for introducing routine prenatal HBsAg screening and prescribing combined passive-active immunization to risk babies. Bangladesh, with a large population and many economic problems, needs a determination of the priority of hepatitis B immunization considering the expenses of universal immunization compared with the immunization cost of risk babies born to HBsAg-positive mothers.

SUBJECTS AND METHODS

The study population consisted of 1,800 pregnant women who delivered from October 1995 to January 1996 at Dhaka Medical College Hospital, the largest public hospital in Bangladesh. The Ethical Committee of the Bangladesh Medical Research Council reviewed and approved the study. Objectives and procedural details of the study were explained to each parturient and informed consent was obtained before enrollment. Using a standard questionnaire, a brief history regarding her socioeconomic condition, antenatal checkup, and risk factors of hepatitis B infection such as history of jaundice, blood transfusion, and surgery, was obtained from each parturient.

In all cases, maternal venous blood and cord blood samples were collected. After initial screening tests of maternal samples for HBsAg, all sera were stored at -25°C . The HBsAg-positive maternal samples were subsequently tested for HBeAg, anti-HBe, total antibody to hepatitis B core antigen (anti-HBc), and IgM anti-HBc. Cord sera from babies born to HBsAg-positive mothers were also tested for HBsAg, HBeAg, and IgM anti-HBc. All positive test results were rechecked and HBsAg-positive test results were confirmed by neutralization assay.

Sera were tested for HBsAg, HBeAg, anti-HBe, total anti-HBc and IgM anti-HBc with commercially available enzyme

TABLE 1

Serologic markers of hepatitis B virus detected in 63 HBsAg-positive parturients*

Anti-HBc, total	Anti-HBc, IgM		HBeAg		Anti-HBe		Both HBeAg and anti-HBe	
	+ ve	- ve/ low	+ ve	- ve	+ ve	- ve	+ ve	- ve
Positive n = 56	2	54	19	37	24	32	0	13
Negative n = 7	0	7	0	7	0	7	0	7
Total n = 63	2	61	19	44	24	39	0	20

* HBsAg = hepatitis B surface antigen; Anti-HBc = anti-body to hepatitis B core antigen; HBeAg = hepatitis B e antigen; Anti-HBe = antibody to hepatitis B e antigen; + ve = positive; - ve = negative.

immunoassays (Sorin Biomedica, Saluggia, Italy). The HBsAg confirmatory test was done using an enzyme immunoassay (Organon Teknika, Boxtel, The Netherlands). All laboratory tests were performed following the manufacturers' instructions.

Associations between groups were analyzed by a chi-square test using the SPSS program (SPSS, Inc., Chicago, IL).

RESULTS

A total of 1,800 pregnant women were screened for HBsAg and 63 were found positive (3.5%, i.e., one in every 29 deliveries). Fifty-four of the 63 HBsAg-positive mothers (85.7%) had serologic evidence of being chronic HBV carriers; 47 were positive for total anti-HBc but negative for IgM anti-HBc, and seven were positive for total anti-HBc but showed a low level of positivity for IgM anti-HBc (sample:cut-off ratio < 2) (Table 1). Only two parturients (3.2%) with high levels of IgM anti-HBc (sample:cut-off ratio > 14) and total anti-HBc were identified as having established acute infections. The remaining seven cases (11.1%) were positive for only HBsAg, representing an uncommon serologic pattern. Of the 63 HBsAg-positive mothers, 19 (30.2%) were found in a highly infective state as indicated by the presence of HBeAg, 24 (38.1%) had anti-HBe, indicating seroconversion, but 20 (31.7%) were negative for both HBeAg and anti-HBe (Table 1).

Among the 63 babies born to HBsAg-positive mothers, 23 had detectable HBs or HBe antigen in cord blood. Seven of 19 babies (36.8%) born to HBeAg-positive mothers showed HBs antigenemia at birth compared with nine of the 44 babies (20.5%) born to HBeAg-negative mothers (Table 2). Cord samples positive for HBsAg also had HBeAg if the

mother was HBeAg positive. Another seven of the 19 babies born to HBeAg-positive mothers (36.8%) were positive for HBeAg alone (Table 2). However, none of the cord sera had IgM anti-HBc. There was no significant association between HBs antigenemia of newborns with the presence of HBeAg ($\chi^2 = 1.88$, $P = 0.17$) and anti-HBe ($\chi^2 = 1.56$, $P = 0.21$) in maternal serum.

Neither demographic features (Table 3) nor risk factors (Table 4) were significantly associated with detection of HBsAg among the parturients. Only 35% of the HBsAg-positive subjects (22 of 63) had any of the risk factors for hepatitis B infection, e.g., history of jaundice, surgery, or blood transfusion. Among HBsAg-positive mothers, 16 (25.4%) had a history of jaundice, five (7.9%) had surgery, and one (1.6%) had both surgery and a blood transfusion. However, none of the clinically jaundiced parturients were positive for HBsAg.

DISCUSSION

Bangladesh has an intermediate prevalence of hepatitis B with a 4% HBsAg-positive population.¹³ In our study 3.5% of the pregnant women were HBsAg positive. Up to now, there are no data on the prevalence of hepatitis B among women of child-bearing age in this country. The observed lower rate among pregnant women is not unexpected because the prevalence of HBsAg is more common among males.^{14, 15} Only two of the HBsAg-positive mothers had established acute infection and seven mothers had HBsAg without anti-HBc, which is an infrequent serologic pattern.¹⁶ Hepatitis B surface antigen is the earliest marker to appear in acute infection and these mothers might have had HBsAg as the only HBV marker at that time. Infection with HBV mutants¹⁷⁻¹⁹ may also be responsible for such serologic findings. However, most of the HBsAg-positive mothers (85.7%) were chronic carriers and a follow-up screening during pregnancy was not essential. To obtain the expected benefits of making HBsAg screening as a part of routine prenatal check-up, the test should be done during late third trimester.

Since all cord blood samples were negative for IgM anti-HBc, intrauterine infection is unlikely. Only the HBsAg particle may be transmitted rather than the whole virus.²⁰ Hepatitis B e antigen is also easily transmitted via the placenta because it is smaller than HBsAg and is not agglutinated.²⁰ Our observation of isolated HBe antigenemia in seven cord blood samples also indicates this possibility. Alternatively, antigenemia in cord samples may result from contamination

TABLE 2

Hepatitis B surface and e-antigenemia detected in cord blood samples of babies born to hepatitis B surface antigen-positive mothers*

HBsAg+ve mothers' samples	Babies' cord blood samples			
	HBsAg + ve HBeAg - ve	HBsAg + ve HBeAg + ve	HBsAg - ve HBeAg + ve	HBsAg - ve HBeAg - ve
HBeAg + ve† (n = 19)	0	7	7	5
HBeAg - ve (n = 44)				
Anti-HBe + ve (n = 24)	4	0	0	20
Anti-HBe - ve (n = 20)	5	0	0	15
Total (n = 63)	9	7	7	40

* HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; Anti-HBe = antibody to hepatitis B e antigen; + ve = positive; - ve = negative. HBsAg (baby) vs. HBeAg (mother): $\chi^2 = 1.8809$; $P = 0.1702$. HBsAg (baby) vs. anti-HBe (mother): $\chi^2 = 1.5595$; $P = 0.2117$.

† All HBeAg-positive mothers were anti-HBe negative.

TABLE 3
Demographic features of HBsAg-positive and HBsAg-negative parturients*

Considered variables	n	HBsAg positive	HBsAg negative	χ^2	P
Age group (years)	1,785	63	1,722	0.480	0.786
<20	520	17 (3.3%)	503 (96.7%)		
21–30	1,107	39 (3.5%)	1,068 (96.5%)		
>30	158	7 (4.4%)	151 (95.6%)		
Ethnic group	1,797			0.931	0.334
Hindu	72	4 (5.6%)	68 (94.4%)		
Muslim	1,725	59 (3.4%)	1,666 (96.6%)		
Family income/month	1,760			3.035	0.219
<2,000 Taka	658	22 (3.3%)	636 (96.7%)		
2,000–5,000 Taka	818	35 (4.3%)	783 (95.7%)		
5,000 Taka	284	6 (2.1%)	278 (97.9%)		
Antenatal checkup	1,739			1.066	0.586
Regular checkup	495	18 (3.6%)	477 (96.4%)		
Irregular checkup	938	31 (3.3%)	907 (96.7%)		
No checkup	306	14 (4.6%)	292 (95.4%)		
Parity	1,773			0.118	0.942
Primaepara	882	32 (3.6%)	850 (96.4%)		
Parity 1–3	791	27 (3.4%)	764 (96.6%)		
Multipara >3	100	4 (4.0%)	96 (96.0%)		

* HBsAg = hepatitis B surface antigen.

by maternal blood at delivery.²¹ However, without a follow-up quantitative estimation of HBsAg and IgM anti-HBc, transient antigenemia cannot be diagnosed.¹⁰ Our result shows no significant association between the proportion of children born with HBs antigenemia and infectivity or seroconversion status of their mothers. If HBsAg in cord blood indicated an infection *in utero*, antigenemia could be found more among babies of HBeAg-positive mothers. Therefore, the presence of HBsAg or HBeAg in the cord blood should not be taken as a contraindication of immunization, but rather that neonatal immunoprophylaxis should be carried out immediately after birth without attempting identification of neonatal antigenemia or intrauterine infection, which involves more expenses and causes delay. Although the risk for neonatal hepatitis B infection is less with HBeAg-negative mothers,^{22–25} infections that occur may be severe^{26, 27} and fulminant hepatitis has been reported.²⁸ Thus, immunization of all infants born to HBsAg-positive mothers regardless of HBeAg status should be done as recommended.^{29, 30}

In our study, risk factors for hepatitis B infection could

be found in only 23 of 63 HBsAg-positive parturients. This low sensitivity argues against use of such historic risk factors in selective maternal screening. Alternatively, screening of all pregnant women provided an opportunity for immunoprophylaxis to one of approximately every 29 infants delivered, which points to the importance of routine antenatal HBsAg screening in prevention of perinatal hepatitis B transmission. This study was carried out in a large urban public hospital, in which health service is offered free. Due to limited facilities and overcrowding, most mothers with normal vaginal delivery leave the hospital shortly after childbirth. To facilitate complete testing of a large population, we used the intrapartum screening strategy and mothers sometimes left the hospital before the laboratory test results were available. In such cases, advising neonatal prophylaxis was delayed and motivation was poor. Therefore, to avoid the delay that decreases efficiency of immunoprophylaxis,³¹ maternal HBsAg should be screened during the antenatal checkup. However, we found that 22.2% (14 of 63) of HBsAg-positive mothers (or 17.6% overall; 306 of 1,739)

TABLE 4
Assessment of risk of hepatitis B virus infection among HBsAg-positive and HBsAg-negative parturients*

Considered variables	n	HBsAg positive	HBsAg negative	χ^2	P
Previous jaundice	1,764			0.083	0.772
No history of jaundice	476	16 (3.4%)	460 (96.6%)		
History of jaundice	1,288	47 (3.6%)	1,241 (96.4%)		
History of surgery	1,763			0.259	0.610
No surgery	1,590	58 (3.6%)	1,532 (96.4%)		
History of surgery	173	5 (2.9%)	168 (97.1%)		
Blood transfusion	1,761			0.425	0.514
Previous transfusion	52	1 (1.9%)	51 (98.1%)		
No transfusion	1,709	62 (3.6%)	1,647 (96.4%)		
Clinical jaundice	1,759			0.599	0.438
Clinically jaundiced	16	0	16 (100%)		
Not jaundiced	1,743	63 (3.6%)	1,680 (96.4%)		

* HBsAg = hepatitis B surface antigen.

did not have any antenatal checkup, but needed intrapartum screening.

Infection at birth or in the perinatal period is the most common mode of hepatitis B transmission in endemic areas, and it is now evident that routine screening of all pregnant women and neonatal vaccination would provide an acceptable control of perinatal transmission.^{2, 10, 11} However, universal immunization is necessary for achieving a maximum control over hepatitis B because selective immunization of risk babies does not prevent the infections during childhood and other horizontal transmissions. It is therefore important to evaluate the cost-effectiveness before initiation of such programs in Bangladesh to allow rational use of the limited resources for health care services. Universal immunization requires three doses of hepatitis B vaccine for all infants, whereas selective immunization requires antenatal HBsAg screening of all pregnant women and three doses of vaccine along with HBIG for the risk babies. The unit cost in universal immunization is the cost of three doses of vaccine. In contrast, the unit cost in selective immunization includes the cost of the HBsAg screening test plus the cost-proportion (% risk babies, i.e., 3.5% in this study) of single passive-active immunization. If we consider only the direct costs, cost-effectiveness will depend on the ratio of children protected from developing the carrier state in the individual approach and the unit cost involvement in the respective option. If no vaccination is done, at the reported rate of 4% HBsAg positivity in the population¹³ and the overall approximately 90% carrier rate among them (85.7% among women and considering more among men), 65 of the 1,800 children born would predictably become chronic hepatitis B carriers. It is assumed that HBeAg-positive, anti-HBe-positive, and HBeAg/anti-HBe negative mothers transmit hepatitis B to their infants in 90%, 12% and 25% of the cases, respectively.²⁹ Based on the prevalence of HBeAg and anti-HBe markers in our study population, approximately 25 infants delivered by 63 HBsAg-positive mothers would acquire perinatal infection and approximately 22 of them (85–90%)^{1, 2} would become chronic hepatitis B carriers. The remaining 43 of the possible 65 carriers would get the infection from other than perinatal transmission. Universal infant immunization would prevent 41 of these 43 carriers (with 95% efficacy)^{32, 33} and also 15 carriers of the perinatal group (with 70% efficacy)^{9, 10, 32, 34} from acquiring the infection, but selective passive-active immunization would prevent 20 carriers (with 90% efficacy)^{2, 9–11} from perinatal infection only. Thus, compared with the selective option, universal immunization would prevent overall 2.80 times more cases (56:20 or 2.80:1). When the unit costs of two options are equal, universal vaccination for preventing hepatitis B carrier would be 2.80 times more cost-effective. Nevertheless, a low priced vaccine^{13, 35} is required for such cost-effectiveness; otherwise, a lower screening cost will shift the calculations in favor of selective immunization. However, considering the nationwide limited facilities for antenatal checkup and laboratory tests, universal vaccination of newborns will be logistically simpler to achieve a better control of HBV infection. We therefore recommend a low-cost hepatitis B vaccine to be included in our expanded program on immunization. Until such a national program can be initiated, routine antenatal

screening and immunoprophylaxis of risk babies should be continued.

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