Proposal for routine antenatal screening at 14 weeks for hepatitis B surface antigen

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Abstract

Objective—To develop a low cost, high compliance screening programme for identification of carriers of hepatitis B surface antigen in the obstetric population of the Netherlands.

Design—A seven year open, descriptive study of screening for hepatitis B surface antigen as part of routine prenatal laboratory testing at 14 weeks of gestation. Compliance with programme evaluated by checking delivery records (hospitals) or registration of births in the 30 participating municipalities (rural area).

Setting—Three large city hospitals (two tertiary referral centres) and one rural area with a large number of home deliveries.

Subjects—99 706 pregnant women applying for prenatal care for the first time.

Main outcome measures—Proportion of pregnant women routinely screened; prevalence of hepatitis B surface antigen in large cities and rural area.

Results—Uptake of screening reached 97% in the hospitals after inclusion of 10% screened at delivery; the estimated uptake in the rural area was >95%. Prevalence of hepatitis B surface antigen was 1.6% in the large cities and 0.3% in the rural area. For screening at delivery the prevalence was 2.5 times higher (4%, $P < 0.01$) than for screening at week 14 of gestation.

Conclusion—Incorporation of universal testing for hepatitis B surface antigen into routine prenatal laboratory testing is practical; high compliance is achieved when screening is supplemented with rapid screening at delivery for those who escaped routine prenatal care.

Introduction

Antenatal care aims at preventing maternal and fetal morbidity. In the Netherlands antenatal care is performed by midwives, general practitioners, and specialists. In many areas up to 50% of antenatal care is in the hands of midwives, who have their own clinics outside the hospital. At 14 weeks of gestation venous blood is routinely checked for blood groups (ABO and rhesus factor) and syphilis. If relevant, antibodies against rubella, toxoplasma, and cytomegalovirus are assessed. Since the availability of hepatitis B vaccine the prevention of perinatal transmission of hepatitis B virus has become feasible. Pregnant women who are positive for hepatitis B surface antigen should be identified before delivery to prevent hepatitis B infection in their neonates by passive or active immunisation, or both.¹⁻³ Therefore, a multicentre study was designed in 1982 to determine whether efficient organisation of screening for hepatitis B could be set up in and outside hospital by adding tests for hepatitis B surface antigen to the already accepted and widely used protocol for routine antenatal screening at 14 weeks of gestation.

This study lasted seven years and preliminary results have already been reported.⁴⁻⁶ The final results of routine antenatal screening for hepatitis B surface antigen in pregnant women, reported here, led to a

proposal for universal screening in the Netherlands; a national programme for such screening was subsequently implemented.

Patients and methods

Three large city hospitals, two in Rotterdam and one in Utrecht, and the rural area of Twente-Gelderse-Achterhoek, where the number of home deliveries is high ($\geq 50\%$), participated in the study. The survey was conducted from July 1982 to October 1989. Permission was obtained from each of the local ethics review boards. All midwives, obstetricians, and general practitioners concerned received written and oral information explaining the purpose of the screening.

At the first visit for antenatal care all pregnant women were asked for informed consent to a test for hepatitis B surface antigen. Each patient had blood collected by venepuncture around the 14th week of pregnancy. The serum was submitted for routine prenatal serological testing for blood groups (ABO and rhesus factor), syphilis, and hepatitis B surface antigen. The surface antigen was measured either by radioimmunoassay (Ausria II, Abbott Laboratories, Chicago) and enzyme linked immunosorbent assay (ELISA) (Auszyme, Abbott Laboratories) in the laboratories associated with the hospitals or by the reversed passive haemagglutination assay (Auscull, Abbott Laboratories) in the regional laboratory. All reactive specimens were confirmed by retesting. The sensitivity of the Auscell assay was considered to be adequate as it missed only two samples positive for hepatitis B surface antigen in a cohort of 100 non-selected women who were positive for the antigen according to Ausria II; both false negative samples had very low titres of hepatitis B surface antigen. All blood samples positive for hepatitis B surface antigen were also tested for hepatitis B e antigen and its antibody (Abbott Laboratories). An additional blood sample from the women positive for hepatitis B surface antigen was obtained at delivery to verify the eligibility of their infants for passive-active immunisation.⁴⁻⁶ The presence of hepatitis B surface antigen in expectant mothers was checked in the delivery rooms in Rotterdam. Whenever a test result was missing, blood was obtained and tested with a rapid haemagglutination test for hepatitis B surface antigen (perinatal screening). Perinatal screening was introduced in 1987 in Utrecht but not in the Twente-Gelderse-Achterhoek region. Data from questionnaires on country of origin, parity, and history of hepatitis were obtained at delivery from all women positive for hepatitis B surface antigen.

To estimate the efficacy of screening, the result of the test for hepatitis B surface antigen in pregnant women was noted in the hospital parturition book. Each month the trial assistant calculated the proportion of pregnant women who had been screened.

In the Twente-Gelderse-Achterhoek region the number of births registered in all 30 municipalities in the study was checked against the list of samples screened at the regional laboratory.

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Statistics—Differences in discrete variables were analysed by Fisher's exact test for small numbers and the χ^2 test. Differences in proportions were calculated by using 95% confidence intervals. Continuous variables were analysed by the Wilcoxon two sample rank sum test.

Results

As the results in the two participating hospitals in Rotterdam were similar they are considered as one centre in Rotterdam. In total, 97% of women were screened for hepatitis B surface antigen with 10% screened at delivery (table I). In the first year screening covered 95% of the hospital population, with 14% screened at delivery. In the final year these figures were 98% and 4%, respectively. For Utrecht, where a perinatal check for hepatitis B surface antigen was not performed initially, a coverage of 87% was reported. At the end of the study period screening covered 91% of the hospital population: 81% at routine screening and 10% at perinatal screening. In the Twente-Gelderse-Achterhoek region the estimated prevalence of screening at the end of the first year of the study was 85%. Later prevalence seemed to be very high; more blood samples from pregnant women were tested than births reported in the study period. Overall, the participating centres screened 99 706 pregnant women for hepatitis

by prenatal or perinatal screening in Rotterdam, such as age, presence of hepatitis B e antigen, country of origin, and parity, were compared. Perinatally screened women were more likely to be primiparous ($P=0.03$; χ^2 test); otherwise there were no significant differences between the two groups.

Of the 705 women positive for hepatitis B surface antigen, 118 (16.7%) were positive for the e antigen. The rate of positive results for hepatitis B e antigen was high for women from East Asia (37%) and Surinam (26%) and similarly low for the other three groups (the Netherlands, 10%; Mediterranean, 10%; other countries, 9%).

All but two women positive for hepatitis B surface antigen seemed to be chronic carriers, as characterised by the presence of the surface antigen in their serum at the time of delivery.

Data from questionnaires on risk factors for hepatitis B were available for analysis from 46 women of Dutch origin at one centre. Only 11.8% (83) of the women positive for hepatitis B surface antigen were of white Dutch origin; of these, 48% (22) had no risk factors, such as a history of transfusions, intravenous drug misuse, (former) resident of an endemic area, member of a family positive for hepatitis B surface antigen, or health care employee in contact with blood.

Most of the women positive for hepatitis B surface antigen had one child during the study period, but 120 had two, 23 had three, and two women had four infants. All but 12 of these 145 women who delivered more than once had the same results in tests for hepatitis B e antigen and antibody; nine women became positive for hepatitis B e antibody, having been positive for the antigen, and three women became positive for hepatitis B e antigen in their next pregnancy.

TABLE I—Prenatal screening for hepatitis B surface antigen in serum samples from pregnant women and rates of positive results per treatment centre

Centre	No of births	No (%) of pregnant women tested	No (%) of women positive for HBsAg
Rotterdam	22 255	21 516 (97)	397 (1.8)
Utrecht	8691	7597 (87)	107 (1.4)
Twente-Gelderse-Achterhoek region	69 530	70 593 (102)	230 (0.3)
Total	100 476	99 706 (99)	734 (0.7)

TABLE II—Annual distribution of number of women screened for and positive for hepatitis B surface antigen in four centres in the Netherlands, 1982-9

Period	Area in which screening took place				No of women positive for HBsAg
	Rotterdam-1	Twente-Gelderse-Achterhoek region	Utrecht	Rotterdam-2	
1982-3	1741	10 263	1033	1388	127
1983-4	1341	10 099	1037	1510	111
1984-5	1449	9731	965	1301	80
1985-6	1551	9827	934	1415	82
1986-7	1713	9746	840	1309	88
1987-8	1572	9074	1239	1398	97
1988-9	1694	9488	1208	1421	99

TABLE III—Characteristics of mothers positive for hepatitis B surface antigen

Characteristic	No (%) of women (n=705)
Age (years):	
15-19	63 (9)
20-24	263 (33)
25-29	187 (27)
30-34	131 (19)
35-39	69 (10)
40-50	19 (3)
HBe status:	
Positive	118 (17)
Negative	586 (83)
Unknown	1 (<1)
Country of origin:	
Netherlands	83 (12)
Mediterranean	377 (53)
Surinam	74 (10)
Asian	102 (14)
Other	69 (10)
Parity:	
Primiparous	226 (32)
Multiparous	476 (68)
Unknown	3 (1)

B surface antigen; 96 972 (97.3%) registered for routine prenatal screening and 2734 (2.7%) women came to the delivery unit without having undergone prenatal screening for the antigen.

The overall prevalence of hepatitis B surface antigen for all participating centres was 0.74%, with some variation throughout the years (table II). The prevalence of the antigen in each centre varied from 1.8% (95% confidence interval 1.7 to 2.0) in Rotterdam to 1.4% (1.1 to 1.7) in Utrecht and 0.3% (0.26 to 0.34) in the Twente-Gelderse-Achterhoek region.

During the study 705 infants were born to mothers positive for hepatitis B surface antigen (table III). In 617 (87.5%) of these mothers the antigen was detected at the time of the first visit to the antenatal clinic. The 88 others (12.5%) came to the delivery unit without having undergone prenatal screening. The rates of those positive for hepatitis B surface antigen for the routinely screened women and the women screened at delivery in Rotterdam were 1.5% (294/19 420) and 4.0% (83/2096) respectively (χ^2 test; $P<0.001$). Characteristics of the women found to be positive

Discussion

Our study clearly shows that the acceptance of routine antenatal screening was excellent. The compliance rate in the hospitals in Rotterdam was 97%. In the rural region indirect evidence suggests that a high rate was reached as there were more pregnant women screened than births registered in the same period.

TIME OF SCREENING

Ideally, the identification of women positive for hepatitis B surface antigen should occur late in the third trimester or at the time of delivery. In the Netherlands screening for the surface antigen at the time of delivery is not an easy task because of the large number of home deliveries. Therefore, the screening programme was implemented as part of routine antenatal care at 14 weeks, being included in the existing protocol of blood testing for ABO and rhesus blood groups and syphilis. This policy led to a high compliance with screening. Since 99% of women positive for hepatitis B surface antigen were also positive at delivery, virtually no child received passive-active vaccination without good reason.

Initially considerable effort was put into educational campaigns that were aimed at the professionals in the participating centres. Little effort was needed to maintain compliance later; one person responsible for a regular check of the implementation of screening in each hospital was sufficient. More effort was needed in the Twente-Gelderse-Achterhoek region, where many professionals were involved.

We observed that perinatal screening was necessary for about 10% of the study population from the large cities, where many patients do not seek antenatal medical care. The relative risk for infection with hepatitis B virus was about 2.5 times higher in women

Key messages

- Mothers who are carriers of hepatitis B surface antigen transmit hepatitis B virus to their offspring perinatally
- Passive-active vaccination of neonates prevents chronic infection with hepatitis B virus effectively
- Universal screening for hepatitis B surface antigen as part of routine prenatal laboratory testing achieved high compliance
- Women without prenatal care but screened at delivery had a twofold higher prevalence of hepatitis B surface antigen (4%) than women with prenatal care (1.8%)
- Universal screening of pregnant women for hepatitis B surface antigen by combined prenatal and perinatal approach is practical and effective in more than 95% of women; it is recommended for prevention of vertical transmission of hepatitis B virus

who had not received routine antenatal care. In Philadelphia, Silverman found the rate of positive results to be eight times higher for pregnant women without antenatal care.⁷

PREVALENCE OF HEPATITIS B SURFACE ANTIGEN

The rate of positive results for hepatitis B surface antigen was 0.7% in our pregnant population; the higher prevalence in the first two years of screening may be explained by the selective inclusion of additional women from high risk groups already in the third trimester of pregnancy. The rate of 0.7% should not be extrapolated to the whole population. Urban hospitals with high prevalences (1.4–1.8%) serve a population that includes high risk ethnic groups, low socioeconomic groups, or both, whereas the Twente-Gelderse-Achterhoek region (prevalence 0.3%) serves a suburban, socioeconomically more privileged population.

The use of the haemagglutination assay in the Twente-Gelderse-Achterhoek region instead of a third generation assay (radioimmunoassay, ELISA) as in the other centres cannot account for the low prevalence of 0.3% in the region: the haemagglutination test detected all but two of a panel of 100 samples positive for the surface antigen according to the third generation test. The two false negative samples had low titres of hepatitis B surface antigen and were unlikely to result in transmission of hepatitis B virus to the offspring.^{8,9} In fact, the test used in this study fulfilled the requirements for a suitable screening test as the tests were simple, were rapidly applicable to large numbers of subjects without discomfort, and had a defined sensitivity and specificity. False negative results were observed in no more than 2% of the samples found to be positive for hepatitis B surface antigen by the third generation assays.

Ethnic origin was the major risk factor for infection with hepatitis B virus in our study. Asian and Mediterranean countries are considered to be of high risk.¹⁰ The prevalence of hepatitis B e antigen among young adults (age 15–45 years) is 30–50% in seropositive subjects from Asia and less than 20% in adults from the Mediterranean.^{11–13} Our findings are in agreement with these reports.

About half (48%) of white Dutch women did not have identifiable risk factors^{14,15} for hepatitis B as defined by the Centers for Disease Control.¹⁶ This figure may be biased owing to loss of some of the questionnaire data from one of the hospitals, but it is certainly not lower than 26%. The findings suggest that about half of the white Dutch carriers would not have been identified without routine screening.

The lower prevalence of 0.3% in the Twente-Gelderse-Achterhoek region is more than five times

that regarded as the cut off point for cost effective screening in the United States (0.06%). On the basis of these results, the Dutch National Health Authorities formulated an official policy on the prevention of perinatal infection with hepatitis B virus by means of routine screening of every woman around 14 weeks of gestation. Laboratories had to add the assay for hepatitis B surface antigen to their prenatal screening package for a nominal sum. As new infections or spontaneous clearance of the surface antigen can occur, women need to undergo renewed testing in subsequent pregnancies. For women who deliver without having had a test for hepatitis B surface antigen, serological testing should be possible on demand. If the laboratory results cannot be made available within 12 hours of delivery the administration of hepatitis B immunoglobulin to the newborn child should be considered. Appointment of someone responsible for the implementation and coverage of screening is advised.

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