

Vertical transmission of hepatitis B virus during pregnancy and delivery in Denmark

Viral Hepatitis Prevention Board

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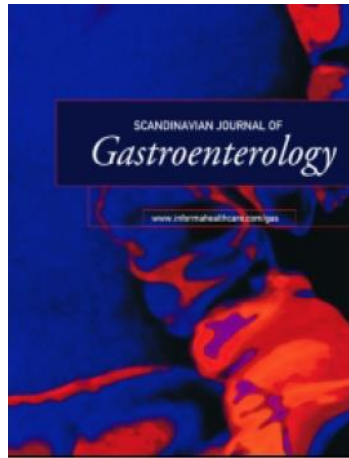


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Background

- Prevalence of Chronic Hepatitis B (CHB) is estimated to be 0.24% (95% CI: 0.23–0.37%) in the Danish population older than 15 years¹
 - Since 2005, pregnant women have been screened for HBV, and children born of HBV infected mothers have been offered hepatitis B Immunoglobulin (HBIG) at birth and vaccination against HBV at birth, and after 1, 2 and 12 months
 - According to Danish guidelines, patients with CHB should be referred to hospital for regular specialized care²
- ¹Hansen N, Hay G, Cowan S, Jepsen P, Krarup HB, Obel N, Weis N, Christensen PB. Hepatitis B prevalence in Denmark - an estimate based on nationwide registers and a national screening program, as on 31 December 2007. Euro Surveill. 2013 Nov 21;18(47).
- ²Christensen PB, Clausen MR, Krarup H, Laursen AL, Schlichting P, Weis N; Danish Society of Infectious Diseases.; Danish Society of Gastroenterology and Hepatology. Treatment for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection - Danish national guidelines 2011. Dan Med J. 2012 Jun;59(6):C4465

Objective

- To determine risk of vertical HBV transmission in children born to mothers with CHB in Denmark
- To investigate the antibody response in the children
- To investigate possible maternal predictive risk factors for HBV transmission

Material & Methods

- Children born of HBV infected women 1. June 2006 - 1. June 2010 were included
- HBV infected women were obtained through The Danish Database for Hepatitis B and C (DANHEP)
- The Danish Civil Registration System – in which all Danish residents are assigned a unique 10-digit Personal Identification Number, was used for identification in various registers
- Surveillance database of all women tested HBV positive in the general pregnancy screening at Statens Serum Institut (or GP or obstetric department)

Material & Methods

- Bloodsamples were tested for HBsAg, anti-HBc, anti-HBs and HBV-DNA.
- HBsAg positive samples were further tested for HBeAg, anti-HBe and HBsAg quantity
- Saliva samples (OraSure collection device) tested for anti-HBc
- Low level of anti-HBs among the children was defined as ≤ 10 IU/L
- High maternal viral load was defined as HBV DNA 10^6 IU/mL

Results

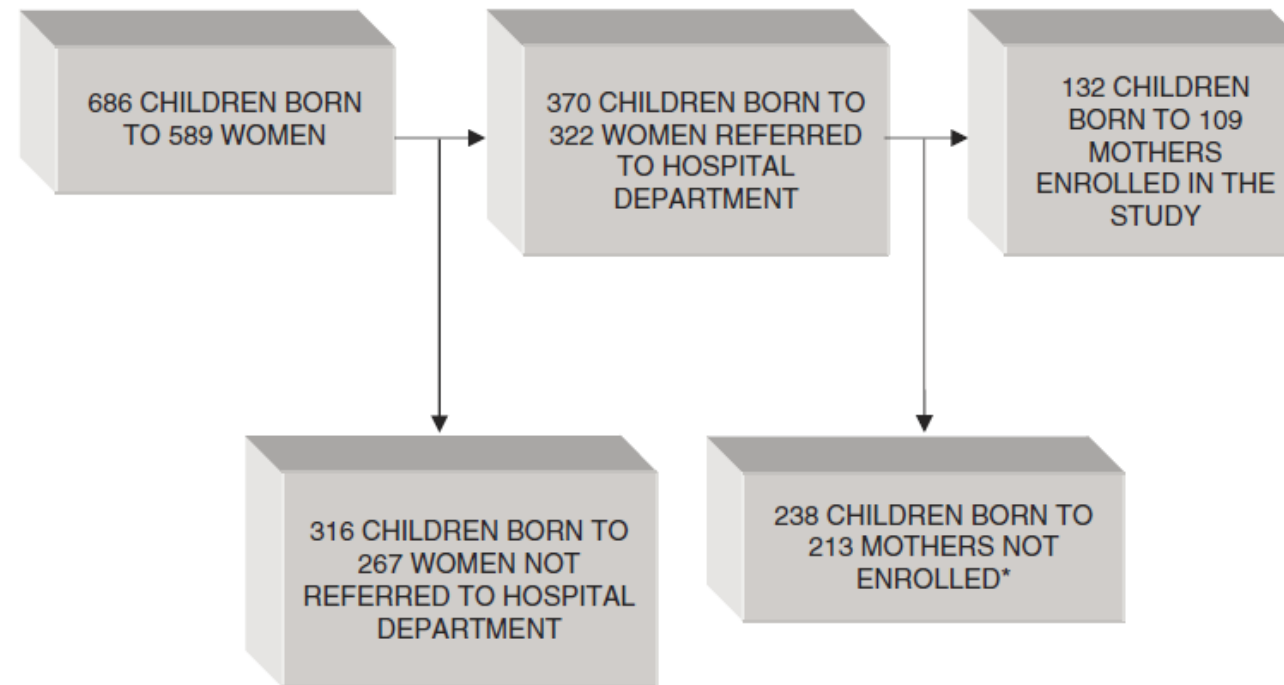


Figure 1. Flowchart of 686 children born in Denmark by 589 hepatitis B virus-infected mothers during 2006–2010. *68 children because the parents did not give consent, three children, because the parents failed to meet with the child for blood sampling, 85 children because the hospital personnel failed to ask the parents for participation, 10 children because attempts at inclusion were unsuccessful (the mother did not adhere to the hospital control visits), 61 children because the mothers never replied to the invitation for the child to participate and 11 children for other reasons.

Results

- Vertical transmission 2.3% in 3/132 enrolled children
(VL 35,000 x 10³ IU/mL; 96,000 x 10³ IU/mL and 150,000 x 10³ IU/mL)
- Among 125 HBsAg-negative children:
19 (15.2%) had been infected but had resolved the infection (anti-HBc-positive, HBsAg-negative)
23 (18.4%) had anti-HBs levels below 10 IU/mL; three of whom were also anti-HBc positive
- No maternal risk factor statistically significantly associated with vertical transmission, although a trend toward positive maternal HBeAg being associated with vertical transmission and missed 4th vaccination being associated with low anti-HBs

Results

- Of the three HBsAg positive children:
- One had been vaccinated according to Danish guidelines
- One had been vaccinated three times, although the two latest vaccinations were given later than recommended (two years after birth with six weeks in between)
- One had received the vaccination at birth only

Results

Table 1. Vaccination status among children born to HBV-infected mothers in Denmark 2006–2010 with known vaccination status.

Variable	Included children, <i>N</i> = 132	Not included children, <i>N</i> = 554	Significance test
Median age at blood sample, years, range	4.2 (1.9; 6.4), <i>N</i> = 128	–	–
Vaccination, at birth	<i>N</i> * = 119	<i>N</i> * = 513	<i>p</i> = .054
Vaccinated, <i>N</i> (%)	117 (98.3%)	481 (93.8%)	–
Unvaccinated, <i>N</i> (%)	2 (1.7%)	32 (6.2%)	–
2nd vaccination	<i>N</i> * = 119	<i>N</i> * = 499	–
Vaccinated, <i>N</i> (%)	115 (96.6%)	457	–
Unvaccinated, <i>N</i> (%)	4 (3.4%)	42	–
3rd vaccination	<i>N</i> * = 116	<i>N</i> * = 493	–
Vaccinated, <i>N</i> (%)	104 (89.7%)	430 (87.2%)	–
Unvaccinated, <i>N</i> (%)	12 (10.3%)	63 (12.8%)	–
4th vaccination	<i>N</i> * = 116	<i>N</i> * = 482	<i>p</i> = .22
Vaccinated, <i>N</i> (%)	81 (69.8%)	310 (64.3%)	–
Unvaccinated, <i>N</i> (%)	35 (30.2%)	172 (35.7%)	–

*Number of children with known vaccination status.

Results

- At study initiation, of 589 eligible women:
- 258 (44%) had been referred to a specialized department and
- 331 (56%) could not be accounted for
- 322 (55%) in total, by encouraging the women's GP's to refer their patients and the departments to search
- 267 (45%) women not referred: 26 emigrated, 7 no address, 1 deceased, 30 discharged, and 203 had apparently never been referred to specialized care

Discussion

- Vertical transmission in Denmark was 2.3% among 132 included children, despite a national vaccination program
- All three HBV infected children had HBIG and were vaccinated at birth, but only one child was correctly vaccinated
- A high proportion of HBsAg-negative children with low levels of anti-HBs (18.4%) and a high proportion with resolved HBV infection (anti-HBc-positive) (15.2%)
- No maternal risk factor statistically significantly associated with vertical transmission
- No HBsAg-negative children with positive HBV DNA (occult infection)
- A large proportion (56%) of mothers with CHB were – in contrast to Danish national guidelines - not referred to specialized hospitalcare

Strengths of the study

- National data with a high degree of completeness
- Nearly all women giving birth during the four-year study period were screened during pregnancy
- Vaccinations given to their children were centrally registered at SSI
- Referred mothers were registered in the nationwide database DANHEP, where status of the mothers HBV infection was also registered
- The PIN facilitates linkage between national registers

Limitations of the study

- The proportion of included children was low (19.7%):
- <50% of the women giving birth during the study period had been referred to specialized care
- A lack of initiative to include children in some centers
- A large proportion of parents who did not want to participate or who did not respond to the invitation
- Blood was drawn from the children at different timepoints after the last vaccination was given

SURVEILLANCE AND OUTBREAK REPORT

Hepatitis B vaccination coverage and risk factors associated with incomplete vaccination of children born to hepatitis B surface antigen-positive mothers, Denmark, 2006 to 2010

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TABLE 1

Country of origin of hepatitis B surface antigen-positive mothers, retrospective cohort study, Denmark, 2006–2010 (n = 594)

Geographical area	Women included in the study	
	n	%
South-east Asia	252	42
The Middle East, northern African countries, including Israel and Turkey	107	18
Sub-Saharan Africa	91	15
Eastern Europe	71	12
Indian subcontinent, including India, Pakistan and Bangladesh	40	7
Denmark	20	3
Greenland	5	< 1
Oceania (Tonga and New Zealand)	2	< 1
South America (Chile and Brazil)	2	< 1
Western Europe (France (n = 1), Spain (n = 2), Sweden (n = 1))	4	< 1

- Vaccination procedures and routines at the sites of delivery with optimal organisation (best practice) should be a model to implement at all sites.
- The sites of delivery should be attentive to mothers of foreign origin but not forget mothers of Danish origin with chronic HBV infection as well as mothers who were themselves adopted.
- It is important that GPs are informed about vaccinations initiated at the hospital and know the plan for subsequent treatment.
- The GP should pay particular attention to ensure that pregnant women with chronic HBV infection attend all prenatal examinations.
- If it becomes known that a child has not received the vaccination series as recommended, the child should be called in for vaccination.
- If the child changes GP, it is important to communicate the HBV vaccination status to the new GP.
- It is important that the GP employ the special provider number for the vaccine, which forms the basis of any assessment of the vaccination coverage nationally.



THANK YOU FOR YOUR ATTENTION