

Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis

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Abstract

Objective To evaluate the effects of hepatitis B vaccine and immunoglobulin in newborn infants of mothers positive for hepatitis B surface antigen.

Design Systematic review and meta-analysis of randomised clinical trials.

Data sources Electronic databases and hand searches.

Review methods Randomised clinical trials were assessed for methodological quality. Meta-analysis was undertaken on three outcomes: the relative risks of hepatitis B occurrence, antibody levels to hepatitis B surface antigen, and adverse events.

Results 29 randomised clinical trials were identified, five of which were considered high quality. Only three trials reported inclusion of mothers negative for hepatitis B e antigen. Compared with placebo or no intervention, vaccination reduced the occurrence of hepatitis B (relative risk 0.28, 95% confidence interval 0.20 to 0.40; four trials). No significant difference in hepatitis B occurrence was found between recombinant vaccine and plasma derived vaccine (1.00, 0.71 to 1.42; four trials) and between high dose versus low dose vaccine (plasma derived vaccine 0.97, 0.55 to 1.68, three trials; recombinant vaccine 0.78, 0.31 to 1.94, one trial). Compared with placebo or no intervention, hepatitis B immunoglobulin or the combination of plasma derived vaccine and hepatitis B immunoglobulin reduced hepatitis B occurrence (immunoglobulin 0.50, 0.41 to 0.60, one trial; vaccine and immunoglobulin 0.08, 0.03 to 0.17, three trials). Compared with vaccine alone, vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (0.54, 0.41 to 0.73; 10 trials). Hepatitis B vaccine and hepatitis B immunoglobulin seem safe, but few trials reported on adverse events.

Conclusion Hepatitis B vaccine, hepatitis B immunoglobulin, and vaccine plus immunoglobulin prevent hepatitis B occurrence in newborn infants of mothers positive for hepatitis B surface antigen.

Introduction

Mother to child transmission of hepatitis B occurs either in utero or through exposure to blood at or around birth. The risk of perinatal transmission is associated with the hepatitis B e antigen status of the mother. If a mother is positive for both hepatitis B surface antigen and e antigen, 70% to 90% of her children become chronically infected.^{1,2} If a mother is positive for the surface antigen only, the risk of transmission is significantly lower.³⁻⁷

The two types of vaccines licensed for hepatitis B are plasma derived vaccine and recombinant vaccine.⁸ Repeated injections over months are required to mount an effective antibody response with vaccination. Hepatitis B immunoglobulin has high levels of

antibody to hepatitis B surface antigen. Treatment with immunoglobulin is immediately effective and seems protective for several months.^{9,10} In the present systematic review, we assessed the beneficial and harmful effects of hepatitis B vaccines and hepatitis B immunoglobulin in newborn infants of mothers positive for hepatitis B surface antigen.

Methods

We included all trials that randomised newborn infants of mothers positive for hepatitis B surface antigen to hepatitis B vaccination and hepatitis B immunoglobulin within the first month of life. We identified randomised trials from several sources (see bmj.com). We scanned reference lists, contacted manufacturers of hepatitis B vaccine, and wrote to the authors of trials with missing data. Our primary outcome measure was the occurrence of hepatitis B, as defined by a blood specimen positive for hepatitis B surface antigen, hepatitis B e antigen, or antibody to hepatitis B core antigen.¹¹ The secondary outcome measures were antibody levels to hepatitis B surface antigen <10 IU/l and adverse events.

We assessed the methodological quality of trials. Trials were post hoc classified as high quality if they had at least two of the following components: adequate generation of allocation sequence, adequate allocation concealment, or adequate blinding. We carried out meta-analyses using a fixed effect model and a random effects model in RevMan analyses 4.2.

Data were analysed by the intention to treat principle, including all randomised participants. Heterogeneity was explored by χ^2 test, with significance set at a P value <0.10. The extent of heterogeneity was measured by I^2 .¹² Metaregression examined the intervention effect in relation to methodological quality of trials, dosage of hepatitis B vaccine and immunoglobulin, and time of injection.¹³ We carried out subgroup analyses according to methodological quality, hepatitis B e antigen status of the mother, and time of injection. We used the test for interaction to estimate the difference between two subgroups.¹⁴ For hepatitis B occurrence we included infants with incomplete or missing data in sensitivity analyses by imputing them into five scenarios (see bmj.com). We used funnel plots to detect publication bias and other biases according to Begg and Egger.



References w1-w38 are on bmj.com



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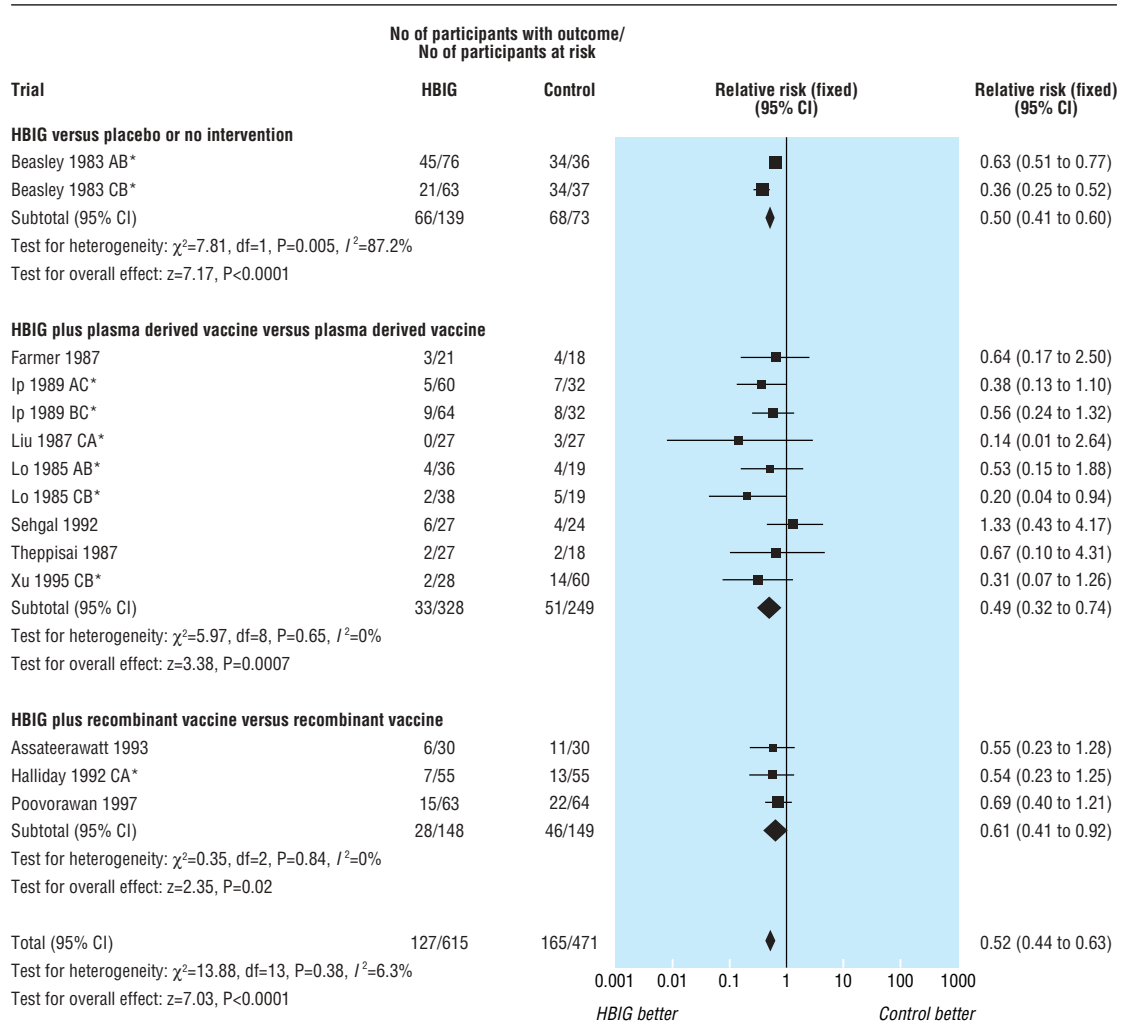


Fig 2 Effect of hepatitis B immunoglobulin (HBIG) on occurrence of hepatitis B in newborn infants. *Experimental and control groups (see bmj.com for definitions)

vaccination, vaccination plus hepatitis B immunoglobulin significantly reduced hepatitis B occurrence (0.54, 0.41 to 0.73; 10 trials). In the meta-regression analyses, none of the trial characteristics was significantly associated with the effect of hepatitis B immunoglobulin. Subgroup analyses did not show a significant difference between high quality and low quality trials, the mother's hepatitis B e antigen status, or time of hepatitis B immunoglobulin injection (tests for interaction, $P=0.70$, 0.62 , and 0.63 , respectively).

Hepatitis B immunoglobulin did not significantly reduce the number of newborn infants with antibody levels to hepatitis B surface antigen <10 IU/l (1.55, 0.89 to 2.73; four trials).

Few trials reported adverse events. In one trial,^{w2} one infant who received hepatitis B immunoglobulin died. The death seemed to be unrelated to the immunoglobulin.

Funnel plots on hepatitis B occurrence showed no asymmetry (Egger test, $P=0.31$; Begg test, $P=0.23$).

Multiple versus single injection of hepatitis B immunoglobulin

Multiple hepatitis B immunoglobulin plus plasma derived vaccine versus single hepatitis B

immunoglobulin injection plus plasma derived vaccine did not significantly reduce the risk of hepatitis B occurrence (0.87, 0.30 to 2.47; two trials, $I^2=0\%$).

Vaccination plus hepatitis B immunoglobulin versus placebo or no intervention

Compared with placebo or no intervention, plasma derived vaccine plus hepatitis B immunoglobulin significantly reduced hepatitis B occurrence (0.08, 0.03 to 0.17; three trials) (see bmj.com). The sensitivity analyses confirmed the robustness of the finding. Subgroup analyses did not find a significant difference between high quality and low quality trials, the mother's hepatitis B e antigen status, or time of hepatitis B immunoglobulin injection (tests for interaction, $P=0.13$, $P=0.28$, and $P=0.22$, respectively).

One trial reported the number of adverse events: 3 out of 71 infants given vaccination versus 5 out of 34 in control group.^{w10} The results showed no significant difference (0.29, 0.07 to 1.13).

Discussion

Our systematic review shows that hepatitis B vaccine, hepatitis B immunoglobulin, or the combination of

What is already known on this topic

Mother to child transmission accounts for up to 50% of hepatitis B carriers

Repeated vaccination over months is required to mount an effective antibody response

Immunoglobulin is immediately effective and seems protective for several months, after which it wanes

What this study adds

Vaccine decreased the risk of hepatitis B infection among infants of mothers positive for hepatitis B surface antigen

Immunoglobulin alone or added to vaccine decreased the risk of hepatitis B infection among infants of mothers positive for hepatitis B surface antigen

Evidence on immunisation for infants of mothers positive for hepatitis B surface antigen but negative for hepatitis B e antigen is weak

vaccine plus immunoglobulin given to the newborn infants of mothers positive for hepatitis B surface antigen prevents the occurrence of hepatitis B. The combination of vaccine plus immunoglobulin was superior to vaccine alone. These benefits were not significantly associated with the methodological quality of the trials, the mother's hepatitis B e antigen status, time of injection, or number of drop outs.

Our review has several potential limitations. Some analyses included few trials and a small number of newborn infants and most trials were of low methodological quality. Although we did not find asymmetries in funnel plots, we cannot exclude publication bias. Most trials only reported surrogate outcomes and not long term clinical outcomes.

Our results show that hepatitis B vaccination prevents the occurrence of hepatitis B in the newborn infants of mothers positive for hepatitis B surface antigen. We found no significant difference between recombinant vaccine and plasma derived vaccine on hepatitis B infections (relative risk 1.00, 95% confidence interval 0.70 to 1.42). However, more infants who received recombinant vaccine achieved antibody levels to hepatitis surface antigen > 10 IU/l (1.96, 1.39 to 2.78).

The recommended schedules for immune prophylaxis against hepatitis B vary among countries.^{15 16} We were unable to show significant differences among different doses, schedules, and forms of plasma derived vaccine and recombinant vaccine on hepatitis B occurrence.

Our meta-analyses found that hepatitis B immunoglobulin alone or when added to hepatitis B vaccine decreased the risk of hepatitis B infection (0.52, 0.44 to 0.63). A recent non-randomised study reported no benefit of adding hepatitis B immunoglobulin to vaccine in mothers negative for hepatitis B e antigen.¹⁷ In our analysis, only one small trial out of 11 trials included infants of such mothers.³³ Our subgroup

analysis did not find any statistically significant difference between infants of mothers negative or positive for hepatitis B e antigen.

Few trials reported sufficiently on adverse events. According to the findings, hepatitis B vaccine and hepatitis B immunoglobulin seem safe. These results are in accordance with two Cochrane reviews on hepatitis B vaccination.^{18 19} Randomised clinical trials may overlook adverse events because of the relatively low numbers of participants or poor reporting of adverse events.²⁰⁻²²

In general, the risk of perinatal transmission from mothers negative for hepatitis B e antigen is considered much lower than that from mothers who are positive for the antigen.³⁻⁷ Our findings are mainly based on immune prophylaxis for infants of mothers positive for hepatitis B surface antigen and hepatitis B e antigen. The applicability of our findings to mothers negative for hepatitis B e antigen is therefore limited.

Two trials that examined a new way to potentially prevent vertical transmission of hepatitis B did not fulfil our inclusion criteria.²³ The trials randomised pregnant women positive for hepatitis B surface antigen to hepatitis B immunoglobulin versus no intervention before delivery.^{24 25} In the group receiving immunoglobulin, fewer infants were positive for hepatitis B surface antigen at follow-up. The methodological quality of those trials was low. More trials are needed before this intervention should be adopted.

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Trends in sexually transmitted infections in general practice 1990-2000: population based study using data from the UK general practice research database

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Abstract

Objective To describe the contribution of primary care to the diagnosis and management of sexually transmitted infections in the United Kingdom, 1990-2000, in the context of increasing incidence of infections in genitourinary medicine clinics.

Design Population based study.

Setting UK primary care.

Participants Patients registered in the UK general practice research database.

Main outcome measures Incidence of diagnosed sexually transmitted infections in primary care and estimation of the proportion of major such infections diagnosed in primary care.

Results An estimated 23.0% of chlamydia cases in women but only 5.3% in men were diagnosed and treated in primary care during 1998-2000, along with 49.2% cases of non-specific urethritis and urethral discharge in men and 5.7% cases of gonorrhoea in women and 2.9% in men. Rates of diagnosis in primary care rose substantially in the late 1990s.

Conclusions A substantial and increasing number of sexually transmitted infections are diagnosed and treated in primary care in the United Kingdom, with sex ratios differing from those in genitourinary medicine clinics. Large numbers of men are treated in primary care for presumptive sexually transmitted infections.

Introduction

Diagnoses of sexually transmitted infections from UK genitourinary medicine clinics have increased considerably since the mid-1990s.¹ The national strategy for

sexual health proposed a shift of services for sexually transmitted infections to primary care in England.² Yet little is known about the contribution of general practice to the diagnosis and management of sexually transmitted infections. It has been reported that 16% of men and 36% of women diagnosed as having chlamydia in the five years to 2000 were last treated in general practice.³ We analysed an anonymised primary care database to explore the contribution of general practice to the diagnosis and management of sexually transmitted infections in the United Kingdom.

Methods

We estimated the incidence of diagnosed sexually transmitted infections between 1990 and 2000 using a retrospective cohort of patients registered in the UK general practice research database, and surveillance data from genitourinary medicine clinics.⁴ The general practice research database contains the records of about 8 million patients, contributing 36 million patient years of observation. Diagnoses in general practice were based on READ or Oxmis codes and in the genitourinary medicine clinics on published KC60 diagnoses. We estimated the incidence of diagnosed sexually transmitted infections in general practice and calculated the proportion of major sexually transmitted infections that were diagnosed in this setting.

To minimise double counting of patients diagnosed in primary care but treated elsewhere, we distinguished patients who were diagnosed and treated in general practice from those who were not treated and

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