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Sangkomkamhang US, Lumbiganon P, Laopaiboon M

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[Intervention Review]

Hepatitis B vaccination during pregnancy for preventing infant infection

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ABSTRACT

Background

Infant hepatitis B infection increases the risk of chronic infection, cirrhosis or liver cancer (hepatocellular carcinoma) in the adult. Perinatal transmission is a common route of infection.

Objectives

To assess the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing hepatitis B virus infection in infants.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2014).

Selection criteria

Randomized controlled trials (RCTs) assessing hepatitis B vaccination compared with placebo or no treatment during pregnancy for preventing infant infection. Quasi-RCTs and cross-over studies were not eligible for inclusion.

Data collection and analysis

Two review authors independently assessed trials for inclusion. If any studies had been included, we planned to assess the risk of bias, extract data and check the data for accuracy of all included studies.

Main results

We did not identify any studies for inclusion.

Authors' conclusions

We found no RCTs that assessed the effects of hepatitis B vaccine during pregnancy for preventing infant infection. Consequently, this review cannot provide guidance for clinical practice in this area. However, it does identify the need for well-designed randomized clinical trials to assess the effect of hepatitis B vaccine during pregnancy on the incidence of infant infection and to determine any adverse effects.

PLAIN LANGUAGE SUMMARY

Hepatitis B vaccination during pregnancy for preventing infant infection

Hepatitis B is an infection caused by the hepatitis B virus and occurs worldwide. For infants and children, the two main sources of the infection are transmission from an infected mother or living in an infected household. Perinatal transmission is common in highly endemic areas. Hepatitis B vaccines are available and require a series of three doses over six months. The most common side effects are pain at the vaccination site and mild to moderate fever. Maternal hepatitis B vaccine immunization may be a way of preventing hepatitis B infection in infants before hepatitis B vaccine can be administered and provide protection to the infant. Infected hepatitis B virus infants are more likely to develop complications such as chronic infection, cirrhosis or liver cancer (hepatocellular carcinoma). This review found no evidence from randomized controlled trials regarding the effects of hepatitis B vaccine for preventing infant infection.

BACKGROUND

Description of the condition

Hepatitis B virus (HBV) is an enveloped, double-stranded DNA virus. Hepatitis B is an infection caused by the HBV and it occurs worldwide. The highest rates of HBV carriers are found in developing countries with limited medical facilities. In highly endemic areas of Asia, Africa and the Pacific, approximately 75% of hepatitis B carriers usually acquire the virus perinatally or in childhood (Safary 2000). In western and northern European countries and in North America, HBV infection is relatively rare and acquired primarily in adulthood. HBV infections result in 500,000 to 1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) (Lavanchy 2004). Globally, HBV causes 60% to 80% of the world's primary liver cancers (Parkin 2001).

Diagnosis of hepatitis is made by biochemical assessment of liver function and coagulation studies (Hollinger 2001). Diagnosis is confirmed by demonstration of specific antigens and/or antibodies. Three clinically useful antigen antibody systems have been identified for hepatitis B: (1) hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs IgG); (2) antibody (anti-HBc IgM) and anti-HBc IgG) to hepatitis B core antigen (HBcAg); and (3) hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe) to determine infectivity.

For infants and children, the two primary sources of HBV infection are perinatal transmission from infected mothers and horizontal transmission from infected household contacts. Perinatal transmission is common in hyperendemic areas, especially when HBsAg carrier mothers are also HBeAg positive (Hollinger 2001; Mahoney 1999). For a newborn infant whose mother is positive for both HBsAg and HBeAg, the risk for chronic HBV infection is 70% to 90% by six months postpartum in the absence of postexposure immunoprophylaxis (Wong 1984). By comparison, the infant risk for chronic infection is less than 10% in the mother who is HBeAg negative (Stevens 1985). Of those persons who are infected with HBV as infants or young children, 25% to 90% become chronic carriers, and approximately 25% of those with chronic infection die prematurely from cirrhosis or liver cancer (hepatocellular carcinoma) (Gitlin 1997; McMahon 1990). Development of chronic HBV infection at an early age increases the risk of HCC more than infection at older age (Hsieh 1992). Nearly 100% of children with HCC were hepatitis B surface antigen seropositive (Chang 1998). Breastfeeding by an HBsAg positive mother does not increase the risk for acquisition of HBV infection in the infant (Beasley 1975).

Description of the intervention

Hepatitis B vaccines are composed of the surface antigen of HBV (HBsAg), and are produced by two different methods: plasma-derived or recombinant DNA (Assad 1999). Plasma-derived vaccines, derived from the plasma of HBsAg-positive donors, consist of highly purified, formalin-inactivated and/or heat-inactivated, alum-adsorbed, hepatitis B subvirion particles (22 nm) of HBsAg that are free of detectable nucleic acid, and, therefore, noninfectious. Recombinant DNA yeast-derived or mammalian cell-derived vaccines, the S gene (pre-S1, pre-S2, S), is cloned and isolated, inserted into an expression plasmid and introduced into yeast or mammalian cells. The desired protein is expressed and assembled into 22 nm antigenic particles. As on natural HBsAg particles, the epitope that elicits the most important immune response is exposed on the surface of artificial particles. Vaccines used for primary prevention have effectively reduced the risk of infection in most populations (Mahoney 1993). Completion of hepatitis B vaccine programs induces protection in about 95% of recipients (Jackson 2007). Vaccination during pregnancy is safe and provides passive transfer of antibodies to the newborn (Anonymous 1991; Gupta 2003; Levy 1991).There are no known side effects from vaccination, in either pregnant women or their offspring (Grosheide 1993). The most common side effects from hepatitis B vaccination are pain at the injection site and mild to moderate fever (Andre 1989; Greenberg 1993).

Hepatitis B vaccine is given into the deltoid muscle by injection in a series of three doses (De Lalla 1988; Krugman 1981). The first shot is given at the elected date; the second dose a month later; and the third dose six months after the first dose. Vaccine batches should be stored at 2° to 8°C. Freezing destroys the potency of the vaccine. Factors that may reduce the immunogenicity of hepatitis vaccines include age (greater than 40 years), weight, genetics, hemodialysis, HIV infection, immunosuppression, tobacco smoking, subcutaneous injection, injection into the buttocks, and accelerated schedule (Ingardia 1999).

How the intervention might work

The mechanism of hepatitis B vaccination during pregnancy for preventing neonatal infection is the production of maternal antibodies that can be transferred across the placenta and provide the neonate with high antibody titers. This could protect the neonate from horizontal infection until active immunization after birth is protective (Reddy 1994).

Why it is important to do this review

Complex HBV epidemiology makes it difficult to evaluate and compare the effectiveness of different immunization policies. HBV infection rates vary in different parts of the world according to the pattern of hepatitis B transmission. In high endemic populations, transmission during delivery is considered for the main mode of perinatal transmission such as close contact with a caregiver who had HBV infection (Ghendon 1987). Many countries have implemented universal hepatitis B immunization at birth, which provides long-term protection against infection in more than 90% of healthy people (Shepard 2006). Despite this, some infants who are born to HBV sero-positive mothers have become infected by HBV despite having received passive-active immunoprophylaxis (Ngui 1998). A prevention program by maternal hepatitis B vaccine immunization may be a way of preventing hepatitis B infection in infants before hepatitis B vaccine can be administered and provide protection. However, the ideal plan for hepatitis B vaccine administration during pregnancy, taking into consideration risk factors (high risk of HBV infection or the general population); endemic populations (high or low); and cost effectiveness, is not known.

OBJECTIVES

To assess the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing HBV infection in infants.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomized controlled trials (RCTs) of hepatitis B vaccination during pregnancy for preventing infant infection. The randomized units could be individual or clustered (e.g. hospitals). Cross-over trials and quasi-randomized trials were not eligible for inclusion.

Types of participants

.All pregnant women who had negative test results of hepatitis B virus serology.

Types of interventions

Hepatitis B vaccine compared with placebo or no treatment.

Types of outcome measures

Primary outcomes

- Incidence of hepatitis B virus infection in infants.

Secondary outcomes

- Hepatitis B antibody for hepatitis B virus (HBs Ab) in newborns up to six months after birth.
- Maternal antibody for hepatitis B virus (HBs Ab).
- Adverse maternal effects such as local reactions at injection site (soreness, swelling, erythema); fatigue; fever; headache.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 August 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* Sangkomkamhang 2011.

For the 2014 update, two review authors independently assessed for inclusion the one report identified as a result of the search strategy and excluded it (Wang 2008) (see Characteristics of excluded studies). If future searches identify trials for inclusion, we will use the methods described in Appendix 1.

RESULTS

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved 13 studies. Eleven studies did not involve hepatitis B vaccine and were excluded. We sought full reports of the remaining two studies for detailed assessment. We identified only one full report of randomized controlled comparison between two doses and three doses of hepatitis B vaccine in pregnancy. The other study was only in abstract form.

Included studies

There are no included trials in this review.

Excluded studies

We excluded 13 studies, mostly because they assessed hepatitis B immunoglobulin (HBIG) for preventing infant hepatitis B infection, or they were not RCTs. One RCT compared two doses versus three doses of hepatitis B vaccine. For details, *see* Characteristics of excluded studies.

Risk of bias in included studies

Not applicable as there are no included studies.

Allocation

Not applicable as there are no included studies.

Blinding

Not applicable as there are no included studies.

Incomplete outcome data

Not applicable as there are no included studies.

Selective reporting

Not applicable as there are no included studies.

Other potential sources of bias

Not applicable as there are no included studies.

Effects of interventions

Not applicable as there are no included studies.

DISCUSSION

Summary of main results

We found no studies to evaluate the effectiveness of hepatitis B virus during pregnancy in preventing neonatal infection.

Overall completeness and applicability of evidence

There are no studies that met our inclusion criteria.

Quality of the evidence

There are no studies that met our inclusion criteria.

Potential biases in the review process

We followed the process of review as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions (* Higgins 2011). There were no conflicts of interest with the review authors.

Agreements and disagreements with other studies or reviews

There are no other reviews and studies related to the efficacy and side effects of hepatitis B vaccine during pregnancy for preventing infant infection.

AUTHORS' CONCLUSIONS

Implications for practice

This review found that there were no randomized controlled trials (RCTs) assessing the effects of hepatitis B vaccine during pregnancy for preventing infant infection. Consequently, this review cannot provide guidance for clinical practice in this area.

Implications for research

This systematic review has identified the need for well-designed RCTs to assess the benefits and adverse effects of hepatitis B vaccine during pregnancy compared with placebo or no treatment for preventing infant infection. The trials should include clinical outcomes of the incidence of hepatitis B virus infection in infants.

There were many studies of using hepatitis B immunoglobulin (HBIG) during pregnancy to prevent neonatal infection. Further meta-analyses are needed to determine the effectiveness and adverse effects of HBIG administered to pregnant women for preventing HBV infection in infants.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, Sangkomkamhang 2011 was been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gupta 2003	Study on immunogenicity and safety of HBV vaccine, comparisons of 2 doses HBV vaccine versus 3 doses in HBsAg negative pregnant women.
Li 2003	Study on 3 comparisons of HBIG versus lamivudine versus no treatment in HBsAg positive pregnant women for prevention of intrauterine infection of HBV.
Li 2004	Study on HBIG versus placebo in HBsAg positive pregnant women for prevention of intrauterine infection of HBV.
Patwardhan 2005	Study on HBV vaccine in both non-pregnant and pregnant women for prevention of vertical transmission. Abstract only.
Wang 2008	Study on HBIG in HBsAg and HBeAg positive pregnant women for prevention of mother to infant HBV transmission.
Xu 2004	Study on lamivudine versus placebo in late pregnancy for mothers with high viremia, in addition to HBV vaccination plus HBIG for the infants for prevention of mother-to-child transmission of HBV.
Xu 2006	Study on HBIG versus placebo in HBeAg and HBsAg positive pregnant women for prevention of intrauterine infection of HBV.
Xu 2009	Study on lamivudine in highly viremic and late pregnancy for prevention of perinatal transmission of HBV infection.
Yu 2003	Study on HBIG in HBsAg positive pregnant women for prevention of intrauterine infection. This was an observational study.
Yuan 2006	Study on 3 doses of HBIG in seropositive for hepatitis B e antigen (HBeAg) pregnant women versus no treatment for prevention of mother-to-child transmission of HBV.
Yue 1999	Study on HBIG in seropositive for hepatitis B surface (HBsAg) antigen pregnant women versus no treatment for prevention of mother-to-child transmission of HBV.
Zhu 1997	Study on HBIG in HBV carriers pregnant women versus no treatment for prevention of mother-to-child transmission of HBV.

Study	Reason for exclusion
Zhu 2003	Study on 3 doses of HBIG in HBsAg carrier pregnant women versus no treatment for prevention of intrauterine transmission of HBV.

HBeAG: hepatitis B e antigen
HBIG: hepatitis B immunoglobulin
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus

APPENDICES

Appendix 1. Methods for data collection and analysis in subsequent updates of this review

Selection of studies

Two review authors will independently assess for inclusion all the potential studies identified as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult the third review author.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult the third review author. We will enter data into Review Manager software (RevMan 2014) and check for accuracy.

When information regarding any of the above is unclear, we plan to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;

- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

The quality of the evidence will be assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons:

1. Incidence of hepatitis B virus infection in infants.

GRADEprofiler (GRADE 2008) will be used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardized mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomized trials

We will include cluster-randomized trials in the analyses along with individually-randomized trials. We will adjust their sample size using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a subgroup analysis to investigate the effects of the randomization unit.

Cross-over trials

Other unit of analysis issues

It is unlikely that cross-over designs will be a valid study design for Pregnancy and Childbirth reviews, and so if identified, we will exclude them.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomized to each group in the analyses, and all participants will be analyzed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if the I^2 is greater than 30% and either the Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses**:**

1. low risk of hepatitis B virus (HBV) infection versus high risk (as defined by authors e.g. injection drug users, healthcare workers) of HBV infection;
2. low endemic setting versus high endemic setting of HBV infection;
3. vaccination schedule (e.g. three doses versus two doses regimen);
4. maternal negative versus positive for marker of hepatitis B virus serology.

The following outcomes will be used in subgroup analysis:

1. Incidence of hepatitis B virus infection in infants.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We plan to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result.

WHAT'S NEW

Date	Event	Description
31 August 2014	New citation required but conclusions have not changed	Review updated. No included studies.
31 August 2014	New search has been performed	Search updated. One new report identified and excluded (Wang 2008).

HISTORY

Protocol first published: Issue 3, 2009
Review first published: Issue 3, 2011

Date	Event	Description
12 April 2011	Amended	Plain language summary heading edited.

CONTRIBUTIONS OF AUTHORS

Ussanee S Sangkomkamhang drafted the review, Pisake Lumbiganon and Malinee Laopaiboon revised and approved the final version of the review (Sangkomkamhang 2011) and the 2014 update.

DECLARATIONS OF INTEREST

Malinee Laopaiboon received an honorarium from the Thailand Research Fund, a non-profit organization.This fund partially subsidizes Thai Cochrane reviewers to do and update Cochrane reviews.

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- Thai Cochrane Network, Thailand.
- Thailand Research Fund (Senior Research Scholar), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods have been updated in accordance with the latest *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Types of participants has been changed from '*All pregnant women unaware of marker results of hepatitis B virus serology*' to '*All pregnant women who had negative test results of hepatitis B virus serology*'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Vaccination; Hepatitis B [*transmission]; Hepatitis B Vaccines [*administration & dosage]; Infectious Disease Transmission, Vertical [*prevention & control]; Pregnancy Complications, Infectious [*prevention & control]

MeSH check words

Adult; Female; Humans; Infant; Pregnancy