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Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage (Review)

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[Intervention Review]

Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage

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ABSTRACT

Background

Preterm infants are at risk of periventricular haemorrhage (PVH). Phenobarbital might prevent ischaemic injury or reduce fluctuations in blood pressure and blood flow in the brain.

Objectives

To assess the benefits and harms of giving phenobarbital to women at risk of imminent very preterm birth with the primary aim of preventing PVH in the infant.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (20 December 2010).

Selection criteria

Randomised trials with reported data that compared neonatal and maternal outcomes following prenatal exposure to phenobarbital, with outcomes in controls with or without placebo.

Data collection and analysis

We independently assessed trial eligibility and quality and extracted data. We included eligible trials in the initial analysis and prespecified sensitivity analyses to evaluate the effect of trial quality.

Main results

Nine trials (1752 women) were included. Analyses of all included trials showed a significant reduction in the rates of all grades of PVH (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.50 to 0.83; nine trials; 1591 women) and severe grades PVH (3 and 4) (RR 0.41, 95% CI 0.20 to 0.85; eight trials; 1527 women) in infants whose mothers had been given prenatal phenobarbital. These results were influenced by trials of poor quality which contributed excessive weight in the analysis due to their higher rates of severe PVH. When only the two higher quality trials were included, these beneficial effects disappeared for all grades of PVH (RR 0.90, 95% CI 0.75 to 1.08; two trials; 945 women), and severe grades of PVH (RR 1.05, 95% CI 0.60 to 1.83; two trials; 945 women).

No difference was found in the incidence of neurodevelopmental abnormalities at paediatric follow up at 18 to 24 months or seven years of age between children born to mothers given prenatal phenobarbital and children not so exposed.

Maternal sedation was more likely in women receiving phenobarbital (RR 2.06, 95% CI 1.79 to 2.37; one trial; 576 women).

Authors' conclusions

The evidence in this review does not support the use of prophylactic maternal phenobarbital administration to prevent PVH in preterm infants or to protect them from neurological disability in childhood. Phenobarbital administration may lead to maternal sedation. If any future trials are carried out, they should measure neurodevelopmental status at follow up.

PLAIN LANGUAGE SUMMARY

Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage

Evidence does not support phenobarbital treatment to women giving birth before 34 weeks to decrease the risk of bleeding into the babies' brains.

Babies born very early (before 34 weeks) are at risk of bleeding in the brain (periventricular haemorrhage). This can be a cause of brain damage that might lead to disability including cerebral palsy. Phenobarbital may prevent injury to the brain by stabilising blood pressure and blood flow in the brain. Possible adverse effects of phenobarbital for the women include drowsiness, gastrointestinal upset and development of a rash.

Nine trials involving 1752 women were included in the review. The trials with low risk of bias found that phenobarbital given to women immediately prior to a very preterm birth did not decrease the risk of bleeding in the brains of the babies. No differences in child development were found on follow up at 18 to 24 months or at seven years.

Maternal sedation was more likely in women receiving phenobarbital. The use of prenatal corticosteroids, known to reduce rates of periventricular haemorrhage, varied between trials and may have influenced findings.

BACKGROUND

Description of the condition

Preterm infants born before 34 weeks' gestation have a significant risk of developing brain injury in association with periventricular haemorrhage (PVH). Severe forms of such lesions are strong predictors of later neurodevelopmental abnormalities, including cerebral palsy.

The exact cause of these lesions is uncertain although it has been hypothesised that brain ischaemia followed by haemorrhage, usually arising initially in the subependymal germinal matrix, is the most likely explanation. Fluctuations in blood pressure and cerebral perfusion around birth and during early postnatal adaptation might also be involved. Most haemorrhages are manifest on head ultrasound within 72 hours of birth although the severity may change after this time (Vohr 2000).

Haemorrhages are usually graded for severity:

- grade 1 - confined to the germinal matrix;
- grade 2 - in the lateral ventricle;
- grade 3 - distending the ventricle;
- grade 4 - intracerebral.

The latter two grades have been associated with long-term neurological sequelae.

Description of the intervention

Intravenous or oral phenobarbital given to women at risk of preterm birth.

How the intervention might work

Phenobarbital is a potential neuroprotective agent that might act by preventing ischaemic injury or by reducing the fluctuations in blood pressure and cerebral perfusion (Goddard 1987; Wimberley 1982). Phenobarbital has been suggested as a postnatal treatment and has been the subject of another Cochrane review (Whitelaw 2007). As many haemorrhages are thought to originate close to the time of birth, prophylactic prenatal rather than postnatal treatment may be preferable. Possible adverse effects for the women of phenobarbital include drowsiness, gastrointestinal upset, and a rash.

For further background and discussion regarding prevention and treatment of PVH, see Horbar 1992.

Why it is important to do this review

PVH has severe effects on the infant's brain and subsequent development. There is a need to identify the most safe and efficacious method to prevent PVH in preterm infants to improve mortality and neurodevelopmental outcomes.

OBJECTIVES

To assess the benefits and harms of phenobarbital administered to women at risk of imminent very preterm birth with the primary aim of preventing periventricular haemorrhage in the infant.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised and quasi-randomised trials with reported data which compared outcomes for women who were given phenobarbital with outcomes for women who were given a different treatment, placebo or no treatment.

Types of participants

Women at risk of imminent very preterm birth (before 34 weeks' gestation).

Types of interventions

Phenobarbital administered to women intravenously or orally before birth with outcomes in controls with or without placebo.

Types of outcome measures

Primary outcomes

- Neonatal mortality;
- early infant death (within three days of life);
- neonatal neurological and other morbidity;
- long-term neurodevelopment;
- maternal morbidity.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (20 December 2010).

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

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

Details of the search strategies for CENTRAL and MEDLINE, 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.

Searching other resources

We also searched the citation lists of relevant publications, review articles and included studies.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third person. We assessed included studies for quality and methodological details without consideration of the results.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors independently extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person. There was no blinding of authorship. We entered data into Review Manager software ([RevMan 2008](#)) and checked for accuracy.

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

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2009](#)). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We described for each included study the methods used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should have produced comparable groups.

We assessed the methods as:

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

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

We described for each included study the method used to conceal the allocation sequence in sufficient detail and determined whether intervention allocation could have been foreseen in advance of, or during recruitment or changed after assignment.

We assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described for each included study all the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

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

We assessed methods as:

- adequate (e.g. where there was no missing data or where reasons for missing data are balanced across groups);
- inadequate (e.g. where missing data are likely to be related to outcomes or are not balanced across groups);
- unclear (e.g. where there is insufficient reporting of attrition or exclusions to permit a judgement to be made).

(5) Selective reporting bias

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

We assessed the methods as:

- adequate (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);
- inadequate (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.

(6) Other sources of bias

We described for each included study any important concerns we had about other possible sources of bias. For example, was there a potential source of bias related to the specific study design? Was the trial stopped early due to some data-dependent process? Was there extreme baseline imbalance? Has the study been claimed to be fraudulent?

We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2009). With reference to (1) and (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar. If significant heterogeneity was found, we explored this by sensitivity analysis followed by random-effects if required.

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measured the same outcome, but used different methods. If there was evidence of skewness, this was reported.

Dealing with missing data

For included studies, we noted levels of attrition. We explored 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 carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed 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 was the number randomised minus any participants whose outcomes were known to be missing.

Where data were not reported for some outcomes or groups, we attempted to contact the study authors for further information.

Assessment of heterogeneity

We applied tests of heterogeneity between trials, if appropriate, using the I^2 statistic. With no significant heterogeneity, we pooled data using a fixed-effect model. If we identified high levels of heterogeneity among the trials (I^2 exceeding 50%), we explored it by prespecified subgroup analysis and performed sensitivity analysis. We used a random-effects meta-analysis as an overall summary if this was considered appropriate.

Assessment of reporting biases

Where we suspected reporting bias (see 'Selective reporting bias' above), we attempted to contact study authors asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, the impact of including such studies in the overall assessment of results was explored by a sensitivity analysis.

Where we suspected publication bias (e.g. where only statistically significant results are reported), this was explored using funnel plots (Higgins 2009). We involved the project statistician in the interpretation of such analysis.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

If we used random-effects analyses, the results were presented as the average treatment effect with its 95% confidence interval, and the estimates of I^2 .

If appropriate, we synthesised data from studies where results are expressed as dichotomous and continuous data. We involved the project statistician before attempting to synthesise different measures of treatment effect.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses based on gestational age or birthweight strata, or both, but were not performed because of insufficient data.

We conducted the following planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001:

1. gestational age;
2. birthweight;
3. gestational age and birthweight.

We were unable to perform the planned subgroup analyses due to insufficient data.

Sensitivity analysis

If we identified high levels of heterogeneity among the trials (I^2 exceeding 50%), we explored it by prespecified subgroup analysis and performed sensitivity analysis. A random-effects meta-analysis was used as an overall summary if this was considered appropriate. This involved analysis based on the rating of selection bias and

attrition bias. This was done by excluding trials given an inadequate rating in the quality assessment for allocation of concealment and then inadequate (20% or more or unclear) for exclusions. We did post hoc sensitivity analysis by removing the trial with dual intervention ([Thorp 1994](#)) in which both phenobarbital and vitamin K were compared with placebo control.

RESULTS

Description of studies

Results of the search

We identified nine trials of prenatal phenobarbital for the prevention of periventricular haemorrhage (PVH) of which all nine met our inclusion criteria. One thousand seven hundred and fifty-two women were recruited into the trials.

Included studies

The nine included randomised controlled trials (RCTs) involved 1752 women ([Detroit 1 1986](#); [Detroit 2 1990](#); [Detroit 3 1996](#); [Italy 1988](#); [Kaempf 1990](#); [Mexico 1998](#); [Morales 1986](#); [Rayburn 1986](#); [Thorp 1994](#)). Some of the RCTs involved more than one intervention. Four trials ([Detroit 1 1986](#); [Detroit 3 1996](#); [Morales 1986](#); [Thorp 1994](#)) used intravenous (IV) followed by oral phenobarbital treatment. Four trials used IV phenobarbital only ([Detroit 2 1990](#); [Italy 1988](#); [Kaempf 1990](#); [Mexico 1998](#)). One study only used oral phenobarbital ([Rayburn 1986](#)). One study ([Thorp 1994](#)) used both vitamin K and phenobarbital as the treatment.

Details of each study are given in the [Characteristics of included studies](#) table.

Excluded studies

No studies identified from the search were excluded from the analysis.

Risk of bias in included studies

Allocation

All except four of the trials ([Detroit 1 1986](#); [Detroit 2 1990](#); [Italy 1988](#); [Morales 1986](#)) used formal randomisation, although the degree of concealment was uncertain in many of the studies ([Kaempf 1990](#); [Mexico 1998](#); [Rayburn 1986](#)). For [Detroit 3 1996](#) and [Thorp 1994](#),

randomisation was in the pharmacy. Allocation concealment was not met in the [Morales 1986](#) trial as they used quasi-randomisation utilising the last digit of the medical record number. In this trial, imbalance in prognostic factors, such as corticosteroid use favouring the treatment group, also suggested non-randomisation.

Blinding

Only the [Detroit 3 1996](#), [Kaempf 1990](#), [Mexico 1998](#) and [Thorp 1994](#) trials were adequately blinded. In the [Rayburn 1986](#) trial, although a placebo was used, this was unblinded at birth to determine the dose of phenobarbital which was given to all neonates. A placebo was not used in the [Detroit 1 1986](#), [Detroit 2 1990](#), [Italy 1988](#), and [Morales 1986](#) trials and were therefore not adequately blinded.

All trials report that the assessment of the primary outcome of PVH was blinded, apart from [Rayburn 1986](#) where this is unclear.

Incomplete outcome data

The rate of exclusion of women after randomisation was high in many of the studies ([Detroit 1 1986](#), 27%; [Detroit 2 1990](#), 31%; [Detroit 3 1996](#), 12%; [Kaempf 1990](#), 29%; [Mexico 1998](#), 12%; [Rayburn 1986](#), 49%; [Thorp 1994](#), 10%). Exclusions were not stated for [Morales 1986](#) and [Italy 1988](#). Furthermore, in one trial ([Detroit 2 1990](#)), the rate of exclusion after randomisation was twice as high in the treatment compared with the control group. The main reason for postrandomisation exclusion was continuation of the pregnancy to 34 weeks and beyond.

The proportion of children lost to follow up at 18 to 36 months for the three trials that reported data were high ([Detroit 2 1990](#), 40 of 136 children randomised, 29%: five deaths, one child diagnosed with trisomy 21, 25 were not assessed at 36 months; [Thorp 1994](#), 293 of 414 children, 71%: 39 deaths, 254 declined 24 month follow up; [Detroit 3 1996](#), 232 of 668 children, 35%: 46 children were born at ≥ 34 weeks' gestation, 51 deaths, 135 did not participate). The proportion of children lost to follow up at seven years for the [Thorp 1994](#) trial was lower (115 of 414 children, 28%: 42 deaths, 73 children not followed up).

See [Figure 1](#) for review authors' judgements about each methodological quality item presented as percentages across all included studies and [Figure 2](#) for review authors' judgements about each methodological quality item for each included study.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Detroit 1 1986	−	?	−	?	+	+
Detroit 2 1990	−	?	−	−	+	+
Detroit 3 1996	?		+	+	+	+
Italy 1988	−	?	−	?	+	−
Kaempf 1990	+	?	+	−	+	+
Mexico 1998	?	?	+	?	+	+
Morales 1986	−	−	−	?	+	−
Rayburn 1986	?	?	?	?	+	?
Thorp 1994	?	?	+	−	+	+

Selective reporting

All included studies were free from selective reporting.

Other potential sources of bias

The [Italy 1988](#) study had more male infants in the treatment group (15) compared to the control group (5). In one study ([Morales 1986](#)), more women in the phenobarbital group (55%) were treated with corticosteroids antenatally compared to the control group (37%). It is uncertain if there is bias in the [Rayburn 1986](#) study as the number of participants in the abstract are different to those reported in the

published article. All other trials were free from other sources of bias ([Detroit 1 1986](#); [Detroit 2 1990](#); [Detroit 3 1996](#); [Kaempf 1990](#); [Mexico 1998](#); [Thorp 1994](#)).

Effects of interventions

We identified nine trials involving 1752 women.

1. Analysis of all trials

Overall there was a significant reduction in the incidence of all grades of PVH (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.50

to 0.83; nine trials; 1591 infants) and in severe grades of PVH (3 and 4) (RR 0.41, 95% CI 0.20 to 0.85; eight trials; 1527 infants) in infants exposed to prenatal phenobarbital using a random-effects model because of significant heterogeneity in the data. This result should be viewed with caution due to the high percentage of postrandomisation exclusions in many of the included studies. The [Morales 1986](#) trial, the one quasi-randomised trial that did not have adequate allocation concealment, strongly influenced that result. When the meta-analysis was plotted with trials in chronological order, there was an apparent reduction in treatment effect with time apart for [Mexico 1998](#). The largest study ([Detroit 3 1996](#)), contributed half of the infants and was assessed by the review authors as having low bias risk. This study found no effect of phenobarbital on the risk of PVH.

There was a significant increase in infant deaths

discharge (RR 3.68, 95% CI 1.14 to 11.87; three trials; 1080 infants) in infants exposed to antenatal phenobarbital compared with those not so exposed but no such difference in stillbirths or death of live born infants prior to discharge between the phenobarbital and control groups. We observed non-significant trends towards a reduction in the combined outcomes of 'early infant death or severe PVH' and 'death before discharge or severe PVH' for infants exposed to prenatal phenobarbital. No differences were seen in other measures of neonatal morbidity.

Three trials reported data on neurodevelopment at paediatric follow up ([Detroit 2 1990](#); [Detroit 3 1996](#); [Thorp 1994](#)). There was no significant difference in Bayley Mental Developmental Index (MDI) scores or in the Bayley Psychomotor Developmental Index (PDI) scores between children exposed to phenobarbital and those not so exposed ([Detroit 3 1996](#); [Thorp 1994](#)). For the [Thorp 1994](#) trial, losses to follow up at two years were 71% and results should be interpreted cautiously. There was a discrepancy between the two published reports on childhood follow up at two years ([Thorp 1997](#); [Thorp 1999](#)). In [Thorp 1999](#), at two years of age, children in the phenobarbital group had significantly lower Bayley MDI scores than children in the control group (mean MDI score 104, standard deviation 21 compared with mean MDI score 113, standard deviation 22). For the [Thorp 1994](#) trial, losses to follow up at seven years were 28% and no significant difference was found between children in the treatment and control groups in developmental outcomes at seven years of age ([Thorp 2003](#)).

In the [Detroit 2 1990](#) and [Detroit 3 1996](#) trials, where the loss to follow-up rates at 18 to 36 month follow up were 29% and 35% respectively, no difference was found in the incidence of neurodevelopmental abnormalities at paediatric follow up at 18 to 36 months of age.

Maternal sedation was more likely in women receiving phenobarbital (RR 2.06, 95% CI 1.79 to 2.37; one trial; 576 women).

2. Pre-specified analyses based on quality of allocation concealment: analysis with the exclusion of the trial not meeting allocation concealment criteria ([Morales 1986](#))

There was still a significant reduction in the risk of all grades of PVH (RR 0.76, 95% CI 0.65 to 0.89; eight trials; 1441 women) but not in severe PVH (RR 0.44, 95% CI 0.19 to 1.01; eight trials; 1379 women), using a random-effects model because of substantial heterogeneity ($I^2 = 52\%$).

There was still a significant increase in infant deaths postdischarge (RR 3.68, 95% CI 1.14 to 11.87; three trials; 1080 infants) in infants exposed to antenatal phenobarbital compared with those not so exposed but no differences in stillbirths, death of live born infants prior to discharge or measures of neonatal morbidity. In the [Detroit 2 1990](#) and [Detroit 3 1996](#) trials no difference was found in the incidence of neurodevelopmental abnormalities at paediatric follow up at 18 to 36 months of age. There was no significant difference in Bayley MDI scores or in the Bayley PDI scores between children exposed to phenobarbital and those not so exposed ([Detroit 3 1996](#); [Thorp 1994](#)). In the [Thorp 1994](#) trial, significantly lower Bayley MDI scores from children in the phenobarbital group compared with the control group were reported at two-year paediatric follow up ([Thorp 1997](#); [Thorp 1999](#)). For the [Thorp 1994](#) trial, at seven years of age no differences were found between children in the treatment and control groups ([Thorp 2003](#)).

The increased risk of maternal sedation remained for women given prenatal phenobarbital (RR 2.06, 95% CI 1.79 to 2.37; one trial; 576 women).

3. Pre-specified analyses based on high-quality trials

This analysis excluded trials with inadequate allocation concealment ([Detroit 1 1986](#); [Detroit 2 1990](#); [Italy 1988](#); [Kaempf 1990](#); [Mexico 1998](#); [Morales 1986](#); [Rayburn 1986](#)) and trials known to have 20% or more postrandomisation exclusions for primary (PVH) outcome ([Detroit 1 1986](#); [Detroit 2 1990](#); [Kaempf 1990](#); [Rayburn 1986](#)) or where the rate of postrandomisation exclusions was unclear ([Italy 1988](#)).

These analyses included the trials of [Thorp 1994](#) and [Detroit 3 1996](#), assessed as of higher methodological quality. Both trials were rated A for allocation concealment and had less than 20% exclusions for the primary outcome of PVH ([Detroit 3 1996](#), 12%; [Thorp 1994](#), 10% postrandomisation exclusions). However, both these trials had exclusions of over 20% for their childhood follow up and so the data for these assessments have not been included in this analysis.

No significant differences were seen in the risk of all grades of PVH (RR 0.90, 95% CI 0.75 to 1.08; two trials; 945 infants) or severe PVH (RR 1.05, 95% CI 0.60 to 1.83; two trials; 945 infants), stillbirths (RR 2.38, 95% CI 0.46 to 12.21; two trials; 1082 infants), death of live born infants prior to discharge (RR 1.42, 95% CI 0.91 to 2.20; two trials; 1075 infants) or infant deaths postdischarge (RR 3.25, 95% CI 0.80 to 13.19; two trials; 953 infants). Similarly, no differences were seen in other measures of neonatal morbidity.

The increased risk of maternal sedation remained for women given prenatal phenobarbital (RR 2.06, 95% CI 1.79 to 2.37; one trial; 576 women).

DISCUSSION

Summary of main results

The apparent benefit of prenatal phenobarbital in preventing periventricular haemorrhage (PVH), shown in earlier studies and in the overall analysis is unlikely to be a true effect of the drug. This is suggested by the disappearance of the effect when only high-quality trials are examined. In addition, there has been an increase in the rate of prenatal corticosteroid use, which is known to reduce rates of PVH ([Roberts 2006](#)). Rates of prenatal corticosteroid use were around 30% in the earlier studies and have increased to 100%

([Thorp 1994](#)) and 60% ([Detroit 3 1996](#)) in some of the more recent trials, although were only 6% in the most recent trial reported ([Mexico 1998](#)). Phenobarbital may be less effective if corticosteroids have been given.

The [Thorp 1994](#) trial was potentially confounded by the use of vitamin K as a co-intervention with phenobarbital. Since vitamin K alone has not been shown to affect the rate of PVH ([Crowther 2010a](#)), this is unlikely to confound the result.

Overall completeness and applicability of evidence

No data are available at present on the effects of phenobarbital when given to women prior to preterm birth at different gestational ages or birthweight strata. It is not recommended that phenobarbital be used in routine practice due to the poor quality of the current evidence and the questionable efficacy of phenobarbital in preventing PVH in the high-quality trial. Also only one trial ([Detroit 3 1996](#)) reported on the incidence of maternal sedation. Maternal side effects must be assessed more completely before phenobarbital is accepted into routine practice.

Quality of the evidence

Poor-quality trials contribute excessively to the weight in the overall analysis due to the higher rate of adverse outcomes in those trials. Others have criticised the poor quality of trials assessing prenatal phenobarbital ([Doyle 1996](#)). The follow-up results of neurodevelopmental outcome are important, yet the results should be viewed with caution since the overall rate of follow up was suboptimal for all trials reporting data (losses to follow up: [Detroit 2 1990](#), 24% of infants at 36 months; [Thorp 1994](#), 71% at two years, and 28% at seven years; [Detroit 3 1996](#), 35% at 18 to 22 months). In addition, there was an imbalance between the treatment and control groups in the ascertainment of women at risk in [Detroit 2 1990](#).

Potential biases in the review process

The largest trial ([Thorp 1994](#)), which was also the best quality trial, had vitamin K as a co-treatment with phenobarbital. Evidence from

the systematic review of trials evaluating prenatal vitamin K prior to preterm birth ([Crowther 2010a](#)) suggests that vitamin K does not influence the rate of PVH.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence in this review does not support the use of prophylactic maternal phenobarbital administration to prevent periventricular haemorrhage in preterm infants or to protect from childhood neurological disability. Phenobarbital administration leads to maternal sedation.

Implications for research

If any future trials are carried out, they should be of high quality, examine the effects of prenatal phenobarbital at gestational ages with a high risk of periventricular haemorrhage, stratify for gestational age and ensure minimal exclusions after randomisation. Neurodevelopmental status at follow up should be measured as the most important outcome.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

[Detroit 1 1986](#)

Methods	Randomised controlled trial.
Participants	63 women < 35 weeks' gestation in threatened preterm labour with a singleton or twin pregnancy. Excluded if barbiturate allergy.
Interventions	500 mg phenobarbital intravenously over 30 minutes, then 100 mg orally every 24 hours (n = 31). The control group received no treatment (n = 32).
Outcomes	Primary outcome: IVH. Other: mortality.
Notes	No information on antenatal steroid usage.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Randomised using a card deck.

Detroit 1 1986 (Continued)

Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	High risk	No placebo used however the assessment of the primary outcome of IVH was blinded.
Incomplete outcome data addressed? All outcomes	Unclear risk	27% (17/63) of women were lost to follow up due to withdrawing from the study, or continuation of the pregnancy to term. 4% (2/49) infants were excluded due to death within 24 hours of birth.
Free of selective reporting?	Low risk	No indication of selective reporting.
Free of other bias?	Low risk	

Detroit 2 1990

Methods	Randomised clinical trial.
Participants	160 women in preterm labour at < 35 weeks with or without ruptured membranes.
Interventions	10 mg/kg (maximum of 100 mg) phenobarbital intravenously over 30 minutes, then 100 mg daily until delivery or 34 weeks (n = 84). The control group received no treatment (n = 76).
Outcomes	Primary outcome: intracranial haemorrhage. Outcomes of follow up at 24-36 months: physical growth, neurologic and developmental outcome.
Notes	Sample size calculation done.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Randomly assigned using a card deck.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	High risk	No placebo was used however the assessment of the primary outcome was blinded.
Incomplete outcome data addressed? All outcomes	High risk	34 of 84 (40%) women randomised into the phenobarbital group were excluded due to cessation of labour, continuation of pregnancy beyond 34 weeks and incomplete infusion of the drug before delivery. However, only 16 of 76 (21%) women randomised to the control group were excluded for those reasons. 21/62 (34%) infants in the phenobarbital group and 19/74 (26%) infants in the control group were excluded from the follow up at 36 months (in total 40/136 (29%) infants at randomisation were excluded). Reasons for exclusion included death postdischarge, failure to keep at least 4 follow up appointments, diagnosis of trisomy and failure to keep the 36 month visit.
Free of selective reporting?	Low risk	No indication of selective reporting.
Free of other bias?	Low risk	

Detroit 3 1996

Methods	Randomised controlled trial.
Participants	610 women 24-33 weeks' gestation who were expected to give birth within 24 hours.
Interventions	10 mg/kg intravenously phenobarbital (n = 309) then, 100 mg phenobarbital or placebo orally until delivery or > 32 weeks or placebo (n = 301).
Outcomes	Primary outcome: intracranial haemorrhage, (only ascertained for liveborn babies born at < 34 weeks (311 in intervention group and 279 in control group), or early death (< 72 hours). Secondary outcomes: maternal side effects, intracranial haemorrhage, periventricular leucomalacia, infant neurodevelopment. Outcomes of follow up at 18-22 months (corrected age): physical growth, neurologic and developmental outcomes.
Notes	Approximately 60% antenatal corticosteroid usage in each group. Trial stopped after 610 women recruited (of a calculated sample size of 1038) as probability of showing a statistically significant treatment effect was unlikely.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomly assigned by a pharmacist.
Blinding? All outcomes	Low risk	Placebo used. Blinded primary outcome assessment.
Incomplete outcome data addressed? All outcomes	Low risk	35/309 (11%) women in the phenobarbital group and 40/301 (13%) women in the placebo group were excluded postrandomisation due to continuation of the pregnancy beyond 33 weeks and delivery prior to initiation of the treatment (12% excluded). Follow up at 18-22 months excluded 118/344 (34%) infants in the phenobarbital group and 114/324 (35%) infants in the placebo group due to delivery after 34 weeks, death before and after discharge from the neonatal intensive care unit, and failure to attend the 18 to 22 month follow-up visit (in total 232/668 (35%) infants at randomisation were excluded).
Free of selective reporting?	Low risk	No indication of selective reporting.
Free of other bias?	Low risk	

Italy 1988

Methods	Randomised trial.
Participants	39 women at risk of imminent risk of preterm birth before 32 weeks' gestation. Excluded: congenital abnormalities, maternal allergy to phenobarb, maternal liver, kidney or renal disease, neonatal birth-weight < 500 g.
Interventions	Phenobarbital IV 2 doses of 350 mg 10 minutes apart, each given over 10 minutes; if not born in 24 hours 250 mg/day in 2 doses (n = 21). Control group received no treatment (n = 18).

Italy 1988 (Continued)

Outcomes	PVH, mortality, other neonatal morbidity.
Notes	Requires author clarification re exclusions, antenatal corticosteroid usage.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Randomised using a card deck.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	High risk	No placebo was used however the primary outcome of PVH was blinded.
Incomplete outcome data addressed? All outcomes	Unclear risk	No information on exclusions.
Free of selective reporting?	Low risk	No indication of selective reporting.
Free of other bias?	High risk	The treatment group included 15 male infants whereas the control group only had 5 males.

Kaempf 1990

Methods	Randomised controlled trial.
Participants	151 women < 31 weeks' gestation in preterm labour or with preterm prelabour rupture of the membranes, or maternal or fetal complication requiring delivery. Excluded if on barbiturates or cardio-respiratory disease, or porphyria.
Interventions	10 mg/kg phenobarbital intravenously (minimum 500 mg maximum 700 mg) over 30 minutes (n = 60). Placebo involved 0.9% saline in equal volume over 30 minutes (n = 50).
Outcomes	Primary outcome: IVH. Other: neonatal mortality, respiratory distress syndrome, Apgar scores.
Notes	Postnatal phenobarbital given if ventilated (91% phenobarbital group, 75% placebo group).

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomly assigned to either the treatment or control group by use of a computer-generated random number list.
Allocation concealment?	Unclear risk	Unclear if number list was concealed.
Blinding? All outcomes	Low risk	A placebo was used. The patient, obstetric, neonatal, nursing and radiology staff were unaware of the treatment allocation. The assessment of the primary outcome was blinded.

Kaempf 1990 (Continued)

Incomplete outcome data addressed? All outcomes	High risk	37% (32/86) of infants randomised to the phenobarbital group were lost to follow up, whereas only 20% (17/84) of those randomised to the placebo group were lost to follow up. Reasons for exclusion included incomplete infusion, delivery after 31 weeks' gestation and neonatal death prior within 24 hours of birth.
Free of selective reporting?	Low risk	No indication of selective reporting.
Free of other bias?	Low risk	

Mexico 1998

Methods	Randomised controlled trial.
Participants	100 women with a singleton pregnancy at 28-32 weeks' gestation at risk of preterm birth. Excluded if taking 'hemostasia' drugs or if they have an autoimmune disease.
Interventions	Those in the phenobarbital group given phenobarbital 10 ug/kg diluted in 100 ul of 5% dextrose solution via a 30-minute infusion (n = 42). Those in the control group given "diluted distilled water dosaged at the same time" (n = 46). Both given at least 4 hours and more than 24 hours before the caesarean section.
Outcomes	Primary outcome: PVH. Secondary outcome: neonatal mortality and morbidity.
Notes	Antenatal steroids only given to 5/88 (6%) women. Reasons for exclusions: stillbirth (1), major congenital malformation (1), no head ultrasound (2), moved hospital (1), technical difficulties in blood sampling (7). No sample size calculation given.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	Low risk	A placebo was used and the assessment of the primary outcome was blinded.
Incomplete outcome data addressed? All outcomes	Unclear risk	12% (12/100) were lost to follow up.
Free of selective reporting?	Low risk	No indication of selective reporting.
Free of other bias?	Low risk	

Morales 1986

Methods	Randomised trial.
Participants	150 women < 32 weeks at imminent risk of delivery (active labour not responding to tocolysis, preterm prelabour rupture of the membranes, or maternal complication). Consent obtained only from treatment group.
Interventions	390 mg intravenously phenobarbital if in active labour, if not in labour 720 mg in 3 oral doses every 4 hours, then 60 mg orally every 6 hours (n = 75). Control group given no treatment (n = 75).
Outcomes	Primary outcome: IVH. Other: respiratory distress syndrome, Apgar scores, need for resuscitation.
Notes	Antenatal steroids given "whenever possible". Phenobarbital used postnatally to all babies (2.5 mg/kg every 12 hours for 4 days).

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Randomly assigned by the last digit of the hospital chart number.
Allocation concealment?	High risk	
Blinding? All outcomes	High risk	No placebo was used however the assessment of the primary outcome was blinded.
Incomplete outcome data addressed? All outcomes	Unclear risk	No exclusions specified.
Free of selective reporting?	Low risk	No indication of selective reporting.
Free of other bias?	High risk	55% (41/75) of patients in the phenobarbital group were given corticosteroids compared with 37% (28/75) in the control group.

Rayburn 1986

Methods	Randomised controlled trial.
Participants	126 women prior to anticipated preterm delivery 26-34 weeks' gestation. Excluded if on anticonvulsants, or if drug abusers, or major congenital abnormality of fetus.
Interventions	Phenobarbital (n = 31) or placebo (n = 33) 30 mg 3 times a day or 90 mg once daily at least 24 hours before birth. All infants given a 6-day maintenance therapy of phenobarbital. Those in the placebo group were given a loading dose of 20 mg/kg.
Outcomes	Primary outcome: IVH.
Notes	Reasons for exclusions postrandomisation: gestational age > 34 weeks, delivered < 24 hours from entry, stopped medication, withdrew.

Risk of bias

Rayburn 1986 (Continued)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomly selected and assigned.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	Unclear risk	Placebo used. Unknown if primary outcome was blinded although unblinding likely in view of differential treatment of neonates.
Incomplete outcome data addressed? All outcomes	Unclear risk	49% (62/126) excluded postrandomisation.
Free of selective reporting?	Low risk	No indication of selective reporting.
Free of other bias?	Unclear risk	Numbers of participants do not match between abstract and main published paper.

Thorp 1994

Methods	Randomised controlled trial stratified by gestational age.
Participants	353 women (414 fetuses) at 24-34 weeks' gestation at risk of spontaneous or indicated preterm birth. All received betamethasone and had ampicillin until known culture negative for GBS.
Interventions	Vitamin K 10 mg intramuscularly. Repeated in 4 days then 20 mg per day orally after 8 days. Pheno-barbital 780 mg intravenously over 90 minutes or 720 mg orally in 3 doses over 8 hours, then 60 mg/6 hours intravenously or oral (n = 177). Versus identical appearing placebo (n = 176).
Outcomes	Primary outcome, PVH; other, neonatal mortality and morbidity. PVH assessed by cranial ultrasound on day 2-3 and day 7 by a radiologist blinded to treatment group. Secondary outcome: infant neurodevelopment. Developmental outcomes at 2 and 7 year follow up.
Notes	Power calculation based on reduction of all PVH 50% to 25% and severe PVH 20% to 5%, needed 200. Interim analysis expanded the sample size because the frequency of severe IVH was substantially lower in the study compared to previous studies. Stopped trial early because baseline risk lower and no difference found.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Block randomisation.
Allocation concealment?	Unclear risk	Randomisation completed by pharmacist.
Blinding? All outcomes	Low risk	Placebo identical to treatment. Phenobarbital levels not followed in treatment group. Blinded assessment of primary outcome.
Incomplete outcome data addressed? All outcomes	High risk	22/203 (11%) babies from the placebo group and 20/211 (9%) babies from the treatment group were lost to follow up initially because they were delivered at or after 34 weeks' gestation (in total 42/414 (10%) infants were excluded).

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Thorp 1994 (Continued)

141/203 (69%) children from the placebo group and 152/211 (72%) children from the treatment group were excluded at 2 years (in total 293/414 (71%) infants randomised were excluded). Reasons for exclusion were antenatal and postnatal demise and mothers declining to be involved in follow up. 52/203 (26%) children in the placebo group and 63/211 (30%) children in the treatment group were lost to follow up at 7 years (in total 115/414 (28%) children randomised were excluded). Reasons for exclusion included antenatal and postnatal demise, and death since discharge.

Free of selective reporting?	Low risk	No indication of selective reporting.
Free of other bias?	Low risk	All patients received betamethasone and ampicillin.

GBS: GBS: group B streptococci
IM: intramuscular
IV: intravenous
IVH: intraventricular haemorrhage
PVH: periventricular haemorrhage

DATA AND ANALYSES

Comparison 1. Phenobarbital versus control - all studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All periventricular haemorrhage (PVH)	9	1591	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.83]
2 Severe (grades 3 and 4) PVH	8	1527	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.20, 0.85]
3 Perinatal mortality	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Stillbirths	2	1082	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [0.46, 12.21]
3.2 Death of live born infants prior to discharge	8	1667	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.76, 1.38]
3.3 Infant deaths post-discharge	3	1080	Risk Ratio (M-H, Fixed, 95% CI)	3.68 [1.14, 11.87]
4 Infant death prior to discharge or severe PVH	2	184	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.07, 2.32]
5 Early infant death or any PVH	3	849	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.22]
6 Early infant death or severe PVH	2	181	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.07, 2.35]
7 Low Apgar score at 5 minutes	5	1297	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.96, 1.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Use of mechanical ventilation	6	804	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.86, 1.20]
9 Respiratory distress syndrome	3	359	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.71, 1.43]
10 Pulmonary air leak	6	818	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.45, 1.31]
11 Patent ductus arteriosus	4	583	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.42]
12 Cerebral palsy at 18-36 months follow up	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.40, 1.28]
13 Cerebral palsy at 7 year follow up	1	299	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.33, 1.76]
14 Other neuromotor impairment at 36 month follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.13, 3.49]
15 Developmental delay at 18-22 months follow up	1	401	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.89, 1.35]
16 Visual impairment at 18-36 months follow up	2	517	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.37, 5.35]
17 Hearing impairment at 18-36 months follow up	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.31, 2.16]
18 Bayley Mental Developmental Index at 18-24 months	2	543	Mean Difference (IV, Random, 95% CI)	-4.21 [-11.89, 3.48]
19 Bayley Psychomotor Developmental Index at 18-24 months	2	538	Mean Difference (IV, Fixed, 95% CI)	-1.82 [-4.71, 1.07]
20 Wechsler Intelligence Scale for Children at 7 year follow up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 Full scale	1	299	Mean Difference (IV, Fixed, 95% CI)	0.30 [-2.92, 3.52]
20.2 Performance	1	299	Mean Difference (IV, Fixed, 95% CI)	1.20 [-2.23, 4.63]
20.3 Verbal	1	299	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.84, 2.64]
21 Wide Range Achievement Test at 7 year follow up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 Reading	1	299	Mean Difference (IV, Fixed, 95% CI)	0.70 [-2.57, 3.97]
21.2 Spelling	1	299	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-3.45, 2.45]
21.3 Mathematics	1	299	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-4.61, 1.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 Achenbach Teacher's Report Form at 7 year follow up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
22.1 Total	1	299	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-3.55, 1.15]
22.2 Internal	1	299	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.82, 1.62]
22.3 External	1	299	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-3.45, 0.45]
23 Child Behavioral Check List total at 7 year follow up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
23.1 Total	1	299	Mean Difference (IV, Fixed, 95% CI)	1.0 [-1.28, 3.28]
23.2 Internal	1	299	Mean Difference (IV, Fixed, 95% CI)	2.0 [-0.10, 4.10]
23.3 External	1	299	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.92, 1.72]
24 Height (cm) at 18-24 months follow up (mean, standard deviation)	1	436	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.75, 0.75]
25 Height < 5th centile at 18-24 month follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.17, 1.42]
26 Weight (kg) at 18-24 month follow up (mean, standard deviation)	1	436	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.38, 0.18]
27 Weight < 5th centile at 18-24 month follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.03, 1.79]
28 Head circumference (cm) at childhood follow up (mean, standard deviation)	1	436	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.53, 0.13]
29 Head circumference < 5th centile at childhood follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.18, 2.52]
30 Maternal sedation	1	576	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.79, 2.37]

Analysis 1.1. Comparison 1 Phenobarbital versus control - all studies, Outcome 1 All periventricular haemorrhage (PVH).

Study or subgroup	Phenobarbital n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Detroit 1 1986	8/25	13/23		9.22%	0.57[0.29,1.11]
Detroit 2 1990	14/62	26/74		11.64%	0.64[0.37,1.12]
Detroit 3 1996	70/311	64/279		19.12%	0.98[0.73,1.32]
			Favours phenobarb 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 1.2. Comparison 1 Phenobarbital versus control - all studies, Outcome 2 Severe (grades 3 and 4) PVH.

Analysis 1.3. Comparison 1 Phenobarbital versus control - all studies, Outcome 3 Perinatal mortality.

Analysis 1.4. Comparison 1 Phenobarbital versus control - all studies, Outcome 4 Infant death prior to discharge or severe PVH.

Analysis 1.5. Comparison 1 Phenobarbital versus control - all studies, Outcome 5 Early infant death or any PVH.

Analysis 1.6. Comparison 1 Phenobarbital versus control - all studies, Outcome 6 Early infant death or severe PVH.

Analysis 1.7. Comparison 1 Phenobarbital versus control - all studies, Outcome 7 Low Apgar score at 5 minutes.

Analysis 1.8. Comparison 1 Phenobarbital versus control - all studies, Outcome 8 Use of mechanical ventilation.

Analysis 1.9. Comparison 1 Phenobarbital versus control - all studies, Outcome 9 Respiratory distress syndrome.

Analysis 1.10. Comparison 1 Phenobarbital versus control - all studies, Outcome 10 Pulmonary air leak.

Analysis 1.11. Comparison 1 Phenobarbital versus control - all studies, Outcome 11 Patent ductus arteriosus.

Analysis 1.12. Comparison 1 Phenobarbital versus control - all studies, Outcome 12 Cerebral palsy at 18-36 months follow up.

Analysis 1.13. Comparison 1 Phenobarbital versus control - all studies, Outcome 13 Cerebral palsy at 7 year follow up.

Analysis 1.14. Comparison 1 Phenobarbital versus control - all studies, Outcome 14 Other neuromotor impairment at 36 month follow up.

Analysis 1.15. Comparison 1 Phenobarbital versus control - all studies, Outcome 15 Developmental delay at 18-22 months follow up.

Analysis 1.16. Comparison 1 Phenobarbital versus control - all studies, Outcome 16 Visual impairment at 18-36 months follow up.

Analysis 1.17. Comparison 1 Phenobarbital versus control - all studies, Outcome 17 Hearing impairment at 18-36 months follow up.

Analysis 1.18. Comparison 1 Phenobarbital versus control - all studies, Outcome 18 Bayley Mental Developmental Index at 18-24 months.

Analysis 1.19. Comparison 1 Phenobarbital versus control - all studies, Outcome 19 Bayley Psychomotor Developmental Index at 18-24 months.

Analysis 1.20. Comparison 1 Phenobarbital versus control - all studies, Outcome 20 Wechsler Intelligence Scale for Children at 7 year follow up.

Analysis 1.21. Comparison 1 Phenobarbital versus control - all studies, Outcome 21 Wide Range Achievement Test at 7 year follow up.

Analysis 1.22. Comparison 1 Phenobarbital versus control - all studies, Outcome 22 Achenbach Teacher's Report Form at 7 year follow up.

Analysis 1.23. Comparison 1 Phenobarbital versus control - all studies, Outcome 23 Child Behavioral Check List total at 7 year follow up.

Analysis 1.24. Comparison 1 Phenobarbital versus control - all studies, Outcome 24 Height (cm) at 18-24 months follow up (mean, standard deviation).

Analysis 1.25. Comparison 1 Phenobarbital versus control - all studies, Outcome 25 Height < 5th centile at 18-24 month follow up.

Analysis 1.26. Comparison 1 Phenobarbital versus control - all studies, Outcome 26 Weight (kg) at 18-24 month follow up (mean, standard deviation).

Analysis 1.27. Comparison 1 Phenobarbital versus control - all studies, Outcome 27 Weight < 5th centile at 18-24 month follow up.

Analysis 1.28. Comparison 1 Phenobarbital versus control - all studies, Outcome 28 Head circumference (cm) at childhood follow up (mean, standard deviation).

Analysis 1.29. Comparison 1 Phenobarbital versus control - all studies, Outcome 29 Head circumference < 5th centile at childhood follow up.

Analysis 1.30. Comparison 1 Phenobarbital versus control - all studies, Outcome 30 Maternal sedation.

Comparison 2. Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All periventricular haemorrhage (PVH)	8	1441	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.65, 0.89]
2 Severe (grades 3 and 4) PVH	8	1379	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.19, 1.01]
3 Perinatal mortality	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Stillbirths	2	1082	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [0.46, 12.21]
3.2 Death of live born infants prior to discharge	7	1517	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.83, 1.55]
3.3 Infant deaths post-discharge	3	1080	Risk Ratio (M-H, Fixed, 95% CI)	3.68 [1.14, 11.87]
4 Infant death prior to discharge or severe PVH	2	184	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.07, 2.32]
5 Early infant death or any PVH	3	849	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.21]
6 Early infant death or severe PVH	2	181	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.07, 2.35]
7 Low Apgar score at 5 minutes	5	1224	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.75, 1.59]
8 Use of mechanical ventilation	7	806	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.86, 1.20]
9 Respiratory distress syndrome	2	209	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.77, 1.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Pulmonary air leak	5	668	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.43, 1.44]
11 Patent ductus arteriosus	3	581	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.42]
12 Cerebral palsy at 18-36 months follow up	2	518	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.58, 1.96]
13 Cerebral palsy at 7 year follow up	1	299	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.33, 1.76]
14 Other neuromotor impairment at 36 month follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.13, 3.49]
15 Visual impairment at 18-36 months follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.16, 5.11]
16 Hearing impairment at 18-36 months follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.02, 10.64]
17 Bayley Mental Developmental Index at 18-24 months	2	543	Mean Difference (IV, Random, 95% CI)	-4.21 [-11.89, 3.48]
18 Bayley Psychomotor Developmental Index at 18-24 months	2	538	Mean Difference (IV, Fixed, 95% CI)	-1.82 [-4.71, 1.07]
19 Wechsler Intelligence Scale for Children at 7 year follow up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 Full scale	1	299	Mean Difference (IV, Fixed, 95% CI)	0.30 [-2.92, 3.52]
19.2 Performance	1	299	Mean Difference (IV, Fixed, 95% CI)	1.20 [-2.23, 4.63]
19.3 Verbal	1	299	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.84, 2.64]
20 Wide Range Achievement Test at 7 year follow up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 Reading	1	299	Mean Difference (IV, Fixed, 95% CI)	0.70 [-2.57, 3.97]
20.2 Spelling	1	299	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-3.45, 2.45]
20.3 Mathematics	1	299	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-4.61, 1.81]
21 Achenbach Teacher's Report Form at 7 year follow up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 Total	1	299	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-3.55, 1.15]
21.2 Internal	1	299	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.82, 1.62]
21.3 External	1	299	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-3.45, 0.45]
22 Child Behavioral Check List total at 7 year follow up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Total	1	299	Mean Difference (IV, Fixed, 95% CI)	1.0 [-1.28, 3.28]
22.2 Internal	1	299	Mean Difference (IV, Fixed, 95% CI)	2.0 [-0.10, 4.10]
22.3 External	1	299	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.92, 1.72]
23 Height (cm) at childhood follow up	1	436	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.75, 0.75]
24 Height < 5th centile at childhood follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.17, 1.42]
25 Weight (kg) at childhood follow up	1	436	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.38, 0.18]
26 Weight < 5th centile at childhood follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.03, 1.79]
27 Head circumference (cm) at childhood follow up	1	436	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.53, 0.13]
28 Head circumference < 5th centile at childhood follow up	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.18, 2.52]
29 Maternal sedation	1	576	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.79, 2.37]

Analysis 2.1. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 1 All periventricular haemorrhage (PVH).

Analysis 2.2. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 2 Severe (grades 3 and 4) PVH.

Analysis 2.3. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 3 Perinatal mortality.

Analysis 2.4. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 4 Infant death prior to discharge or severe PVH.

Analysis 2.5. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 5 Early infant death or any PVH.

Analysis 2.6. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 6 Early infant death or severe PVH.

Analysis 2.7. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 7 Low Apgar score at 5 minutes.

Analysis 2.8. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 8 Use of mechanical ventilation.

Analysis 2.9. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 9 Respiratory distress syndrome.

Analysis 2.10. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 10 Pulmonary air leak.

Analysis 2.11. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 11 Patent ductus arteriosus.

Analysis 2.12. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 12 Cerebral palsy at 18-36 months follow up.

Analysis 2.13. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 13 Cerebral palsy at 7 year follow up.

Analysis 2.14. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 14 Other neuromotor impairment at 36 month follow up.

Analysis 2.15. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 15 Visual impairment at 18-36 months follow up.

Analysis 2.16. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 16 Hearing impairment at 18-36 months follow up.

Analysis 2.17. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 17 Bayley Mental Developmental Index at 18-24 months.

Analysis 2.18. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 18 Bayley Psychomotor Developmental Index at 18-24 months.

Analysis 2.19. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 19 Wechsler Intelligence Scale for Children at 7 year follow up.

Analysis 2.20. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 20 Wide Range Achievement Test at 7 year follow up.

Analysis 2.21. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 21 Achenbach Teacher's Report Form at 7 year follow up.

Analysis 2.22. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 22 Child Behavioral Check List total at 7 year follow up.

Analysis 2.23. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 23 Height (cm) at childhood follow up.

Analysis 2.24. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 24 Height < 5th centile at childhood follow up.

Analysis 2.25. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 25 Weight (kg) at childhood follow up.

Analysis 2.26. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 26 Weight < 5th centile at childhood follow up.

Analysis 2.27. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 27 Head circumference (cm) at childhood follow up.

Analysis 2.28. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 28 Head circumference < 5th centile at childhood follow up.

Analysis 2.29. Comparison 2 Phenobarbital versus control - excluding trial with non-concealment at randomisation (C quality), Outcome 29 Maternal sedation.

Comparison 3. Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All periventricular haemorrhage (PVH)	2	945	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.08]
2 Severe (grades 3 and 4) PVH	2	945	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.60, 1.83]
3 Perinatal mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Stillbirths	2	1082	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [0.46, 12.21]
3.2 Death of live born infants prior to discharge	2	1075	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.91, 2.20]
3.3 Infant deaths post-discharge	2	953	Risk Ratio (M-H, Fixed, 95% CI)	3.25 [0.80, 13.19]
4 Early infant death or any PVH	1	668	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.79, 1.37]
5 Low Apgar score at 5 minutes	2	1040	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.82, 1.82]
6 Use of mechanical ventilation	1	372	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.12]
7 Pulmonary air leak	1	372	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.41, 4.95]
8 Patent ductus arteriosus	1	372	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.42, 2.13]
9 Maternal sedation	1	576	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.79, 2.37]

Analysis 3.1. Comparison 3 Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions), Outcome 1 All periventricular haemorrhage (PVH).

Analysis 3.2. Comparison 3 Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions), Outcome 2 Severe (grades 3 and 4) PVH.

Analysis 3.3. Comparison 3 Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions), Outcome 3 Perinatal mortality.

Analysis 3.4. Comparison 3 Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions), Outcome 4 Early infant death or any PVH.

Analysis 3.5. Comparison 3 Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions), Outcome 5 Low Apgar score at 5 minutes.

Analysis 3.6. Comparison 3 Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions), Outcome 6 Use of mechanical ventilation.

Analysis 3.7. Comparison 3 Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions), Outcome 7 Pulmonary air leak.

Analysis 3.8. Comparison 3 Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions), Outcome 8 Patent ductus arteriosus.

Analysis 3.9. Comparison 3 Phenobarbital versus control - high-quality trials only (A for allocation concealment and < 20% exclusions), Outcome 9 Maternal sedation.

WHAT'S NEW

Date	Event	Description
20 December 2010	New search has been performed	Format updated; search updated, no new trials added.

HISTORY

Protocol first published: Issue 1, 1997

Review first published: Issue 1, 1997

Date	Event	Description
11 November 2009	New citation required but conclusions have not changed	New author helped prepare the last update.
14 April 2008	Amended	Converted to new review format.
30 March 2008	New search has been performed	Search updated. Thorp 2003 study found which is a follow-up report on the Thorp 1994 trial - this reports developmental outcomes in children at age seven.
19 March 2003	New search has been performed	Search updated. Three new references found relating to existing included trials. No new trials. One publication awaiting assessment which appears to be an additional report of Thorp 1994 .
30 September 2000	New search has been performed	Search updated. Three new references found, including one new trial.

CONTRIBUTIONS OF AUTHORS

CA Crowther (CAC) and D Henderson-Smart (DHS) contributed to the development of the original protocol, identification and selection of trials for inclusion, data extraction and prepared the update in 2003.

For the 2008 update, CAC and DD Crosby (DDC) assessed the new studies for inclusion and performed the data extraction. DDC drafted the changes to the text and prepared subsequent drafts. CAC and DHS contributed to the drafts.

For the 2011 update, DDC drafted the changes to the text and prepared subsequent drafts. CAC contributed to the drafts and final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.
- NSW Centre for Perinatal Health Services Research, University of Sydney, Australia.

External sources

- Australian Government. Department of Health and Ageing, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Central Nervous System Agents [*therapeutic use]; Cerebral Hemorrhage [*prevention & control]; Cerebral Ventricles; Infant, Premature, Diseases [*prevention & control]; Obstetric Labor, Premature; Phenobarbital [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy