Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

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TABLE OF CONTENTS

[Intervention Review]

Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

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ABSTRACT

Background

Immediate delivery of the preterm fetus with suspected compromise may decrease the risk of damage due to intrauterine hypoxia. However, it may also increase the risks of prematurity.

Objectives

To assess the effects of immediate versus deferred delivery of preterm babies with suspected fetal compromise on neonatal, maternal and long-term outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (27 February 2012).

Selection criteria

Randomised trials comparing a policy of immediate delivery with deferred delivery or expectant management in preterm fetuses with suspected *in utero* compromise. Quasi-randomised trials and trials employing a cluster-randomised design were eligible for inclusion but none were identified.

Data collection and analysis

Two review authors independently evaluated trials for inclusion into the review. Two review authors assessed trial quality and extracted data. Data were checked for accuracy.

Main results

We included one trial of 548 women (588 babies) in the review. There was no difference in the primary outcomes of extended perinatal mortality (risk ratio (RR) 1.17, 95% confidence interval (CI) 0.67 to 2.04) or the composite outcome of death or disability at or after two years (RR 1.22, 95% CI 0.85 to 1.75) with immediate delivery compared to deferred delivery. More babies in the immediate delivery group were ventilated for more than 24 hours (RR 1.54, 95% CI 1.20 to 1.97). There were no differences between the immediate delivery and deferred delivery groups in any other individual neonatal morbidity or markers of neonatal morbidity (cord

pH less than 7.00, Apgar less than seven at five minutes, convulsions, interventricular haemorrhage or germinal matrix haemorrhage, necrotising enterocolitis and periventricular leucomalacia or ventriculomegaly).

More children in the immediate delivery group had cerebral palsy at or after two years of age (RR 5.88, 95% CI 1.33 to 26.02). There were, however, no differences in neurodevelopment impairment at or after two years (RR 1.72, 95% CI 0.86 to 3.41) or death or disability in childhood (six to 13 years of age) (RR 0.82, 95% CI 0.48 to 1.40). More women in the immediate delivery group had caesarean delivery than in the deferred delivery group (RR 1.15, 95% CI 1.07 to 1.24). Data were not available on any other maternal outcomes.

Authors' conclusions

Currently there is insufficient evidence on the benefits and harms of immediate delivery compared with deferred delivery in cases of suspected fetal compromise at preterm gestations to make firm recommendations to guide clinical practice. Where there is uncertainty whether or not to deliver a preterm fetus with suspected fetal compromise, there seems to be no benefit to immediate delivery. Deferring delivery until test results worsen or increasing gestation favours delivery may improve the outcomes for mother and baby. More research is needed to guide clinical practice.

PLAIN LANGUAGE SUMMARY

Immediate or deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

When there is concern that a baby in the womb may not be receiving enough oxygen or nutrients, the choice is to deliver the baby immediately following a course of steroids to help the baby's lungs to mature or to wait as long as is thought to be safe. Waiting allows the baby to develop as much as possible and decreases the risks associated with prematurity. Immaturity of the newborn can lead to respiratory distress, hypothermia (reduced body temperature), low blood sugar levels, infection and jaundice. Remaining in the womb may mean the baby experiences damage of vital organs from the lack of oxygen. The aim of this review was to assess which management option was better for mothers and babies.

We included one randomised study that involved 548 pregnant women (and 588 babies) with pregnancies between 24 and 36 weeks' gestation. The study was performed in 13 countries, between 1993 and 2001. Women were included if their doctor was concerned about the developing baby but unsure if immediate delivery was indicated. The women were randomly allocated to immediate delivery or delivery when the doctor considered that it was necessary.

For preterm babies with suspected fetal compromise and uncertainty about whether to deliver or not, there appears to be no benefit to immediate delivery. There was no difference in death or disability at two years of age between the groups. More women in the immediate delivery group were delivered by caesarean section and more babies delivered immediately required mechanical ventilation for longer than 24 hours. The number of infants with cerebral palsy at two years of age was also higher in the immediate delivery group but there was no differences in neurodevelopment impairment at or after two years, or death or disability in childhood (six to 13 years of age). Deferred delivery may be preferable, but further studies need to be performed to confirm these findings ant to determine any differences neonatal deaths. The difference in the median time between randomisation and delivery in the two groups was four days.

BACKGROUND

Description of the condition

Fetal compromise occurs when there is an inadequate oxygen or nutrient supply to the developing baby. This can be recognised by progressive alterations in the growth, metabolic, cardiovascular and behavioural parameters of the fetus, which represent increasing hypoxaemia and acidosis. The function of vital organs may be affected, leading to temporary or permanent damage or intrauterine death. Fetal compromise is most commonly a result of placental insufficiency, which occurs in approximately 3% of pregnancies (Alberry 2007). This is thought to originate from defective trophoblast invasion in the first trimester (Miller 2008), leading

to increased placental vascular resistance that impairs oxygen and nutrient supply to the fetus. Other causes include congenital abnormality, isoimmunisation, intrauterine infection and twin-twin transfusion syndrome in monochorionic twins. The degree and progression of fetal compromise is variable, and is probably dependent on gestation, maternal factors and the nature and severity of the underlying cause (Miller 2008).

A number of interventions have been proposed as *in utero* treatments for fetal compromise, including calcium channel blockers, hormones, steroids, nutritional supplementation, oxygen therapy, plasma volume expansion, abdominal decompression, electrostimulation, betamimetics and bed rest. Many of these have been reviewed in other Cochrane Reviews and none have been found to be effective in improving outcome (Hofmeyr 1996; Say 1996a; Say 1996b; Say 1996c; Say 1996d; Say 2001; Say 2003a; Say 2003b; Say 2003c). An exception is in cases of compromise due to twin-twin transfusion syndrome. This is a distinct condition where compromise arises due to vascular anastomoses in the placental circulation of monochorionic twins. In this situation there is some evidence that laser coagulation of anastomotic vessels improves perinatal outcome (Roberts 2008), hence we have excluded this group from this review. In all other situations leading to fetal compromise, in the absence of effective interventions, the mainstay of management is based on monitoring progression of fetal compromise and delivering the baby at a time that is thought to minimise risk to the infant.

Deciding the optimal timing for delivery of preterm babies with fetal compromise is often difficult. Immediate delivery removes the baby from the hostile uterine environment, decreasing the risk of damage due to hypoxia. However, these benefits must be offset against the risks of increased morbidity and mortality associated with premature delivery. The earlier the gestation at delivery, the greater the risk to the baby of developing complications (Iacovidou 2010). Immaturity of neonatal homeostatic mechanisms predispose preterm babies to respiratory distress, hypothermia, hypoglycaemia, infection and jaundice. The incidence of serious morbidities increases as gestation decreases, including chronic lung disease, necrotising enterocolitis, retinopathy of prematurity, intraventricular haemorrhage and periventricular leukomalacia, which all can lead to death or long-term disability. In survivors, there is also an apparent dose response between gestation at delivery and cerebral palsy, intellectual impairment and behavioural problems.

The presentation of fetal compromise is variable. Recognition of the pregnancy at risk of fetal compromise may be based on clinical features, such as obstetric history or the presence of medical conditions associated with placental insufficiency. Abnormal fetal growth or liquor production may be found on abdominal palpation, or on ultrasound examination. A decrease in fetal movements may be perceived by the mother, or fetal heart rate abnormalities may be detected on cardiotocograph (CTG).

Several different methods can be used to assess fetal compromise including the following.

- Serial ultrasound biometry (Bricker 2009), which can detect reduction in fetal growth velocity. This is often performed in conjunction with ultrasound assessment of amniotic fluid, which if reduced may reflect reduction in fetal urine production secondary to reduced renal blood flow which occurs as a physiological response to poor placental blood flow.
- Umbilical artery Doppler ultrasound (Alfirevic 2010), which can detect increased resistance or absent or reversed end-diastolic flow. This reflects increasing placental vascular resistance and damage.
- Fetal arterial Doppler ultrasound (e.g. middle cerebral artery or aortic isthmus) (Alfirevic 2010), which can detect decreased resistance, indicative of brain sparing.
- Fetal venous Doppler ultrasound (e.g. ductus venosus or inferior vena cava) (Alfirevic 2010). Abnormalities reflect pre-terminal impairment of cardiac function.
- CTG (Grivell 2010), which can detect changes in fetal heart reactivity.
- Computerised CTG (Guzman 1996), which can detect changes suggestive of fetal hypoxaemia and acidaemia.
- Biophysical profile (Lalor 2008), which consists of CTG in combination with ultrasound to detect changes in fetal behaviour and reduction in amniotic fluid volume that can occur secondary to decreased renal blood flow and fetal urine production. The combination of CTG and amniotic fluid volume assessment alone is called the modified biophysical profile.

The diagnosis of fetal compromise, and the uncertainties in its management can be very distressing for women and their families. Suspected or proven fetal compromise is likely to increase anxiety about pregnancy outcome, and the need for intensive monitoring or admission can be disruptive and result in separation from the family.

Description of the intervention

Once fetal compromise is recognised, the options are immediate delivery (with or without awaiting 24 to 48 hours for administration of antenatal steroids to promote fetal lung maturity) or expectant management. Expectant management involves monitoring progression of fetal compromise and, if monitoring is sufficiently reassuring, either allowing pregnancy to continue to a certain gestational age or the onset of spontaneous labour, or delivering the fetus when it is thought that the degree of *in utero* compromise imminently jeopardises fetal well-being. Fetal monitoring can involve any of the methods described above, and a combination of methods are often used. Other Cochrane Reviews (Alfirevic 2010; Grivell 2009; Lalor 2008; Nabhan 2008) focus on methods and frequency of assessing fetal compromise. Delivery is most often achieved by caesarean section, although occasionally induction of labour may be attempted.

Why it is important to do this review

Despite advances in technology for recognition of fetal compromise, considerable controversy surrounds whether a policy of immediate or deferred delivery provides the best outcome for these infants. Evidence regarding the risks and benefits of each approach is needed to direct management decisions for women with suspected fetal compromise.

OBJECTIVES

To assess the effects of immediate versus deferred delivery of preterm babies with suspected fetal compromise on neonatal, maternal and long-term outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials and quasi-randomised trials, including cluster-randomised trials, comparing a policy of immediate delivery with deferred delivery or expectant management in preterm fetuses with suspected *in utero* compromise.

Types of participants

Pregnant women at less than 36 weeks' gestation in whom there is clinical suspicion of fetal compromise as defined by trialists.
Outcomes of pregnancies with fetal compromise diagnosed after 36 weeks' gestation are the focus of another Cochrane Review (Bond 2011).
We included multiple pregnancies. We intended to separate monochorionic and dichorionic twins where possible and exclude women with twin-twin transfusion syndrome. This is because interventions are available that are thought to improve outcome in twin-twin transfusion, so expectant management is less relevant. However, this information was not available.

Types of interventions

Immediate delivery or deferred delivery. Immediate delivery may be by induction of labour or caesarean section. It may or may not include time for a course of effective antenatal steroids (48 hours). Deferred delivery may be for a set period of time, until test results worsen, or expectant management (waiting for spontaneous labour).

Types of outcome measures

Primary outcomes

1. Extended perinatal mortality (intrauterine death or death in the first 28 days of life).
2. Serious neonatal morbidity (composite outcome including bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), hypoxic Ischaemic encephalopathy (HIE).
3. Death or disability at or after two years of age.

Secondary outcomes

Perinatal

1. Stillbirth (intrauterine death of fetus at more than 24 weeks' gestation)
2. Neonatal mortality (death of a baby born with signs of life within 28 days of birth).
3. Postneonatal mortality (death of a baby greater than 28 days up to one year of life).

Fetal/neonatal

1. Cord pH less than 7.0.
2. Apgar less than seven at five minutes.
3. Apgar less than four at five minutes.
4. Any admission to neonatal intensive care or special care facility.
5. Any resuscitation required.
6. Intubation/ventilation required.
7. Interval between randomisation and delivery.
8. Gestation less than 28 weeks at delivery.
9. Gestation less than 34 weeks at delivery.
10. Birthweight less than tenth centile.
11. Birthweight less than fifth centile.
12. Birthweight less than third centile.
13. Low birthweight (less than 2.5 kg).
14. Very low birthweight (less than 1.5 kg).
15. Respiratory distress syndrome (as defined by trialists).
16. Meconium aspiration (as defined by trialists).
17. Seizures (as defined by trialists).
18. Infection or sepsis (as defined by trialists).
19. Neonatal cooling performed.
20. Any HIE (grade I, II or III).
21. Moderate or severe HIE (grade II or grade III).
22. IVH or germinal matrix haemorrhage (GMH).
23. BPD.
24. NEC (as defined by trialists).
25. ROP requiring treatment.

26. Periventricular leucomalacia (PVL) or ventriculomegaly.
27. Length of hospital stay.

Maternal

1. Caesarean section.
2. Induction of labour.
3. Spontaneous vaginal birth.
4. Operative vaginal birth.
5. Breastfeeding.
6. Maternal satisfaction with care.
7. Antenatal admission (days).
8. Any antenatal complication (pre-eclampsia, thromboembolic disease, antepartum haemorrhage, infection, other).
9. Administration of antenatal corticosteroids.

Long-term outcomes

1. Neurodevelopmental impairment at or after two years of age.
2. Cerebral palsy at or after two years of age.

Non-prespecified outcomes

We also reported the following additional outcomes that we considered to be important. These were not prespecified in our protocol.

1. Death at or after two years of age.
2. Kaufman-Assessment Battery for Children Mental Processing Component Score in childhood.
3. Death or severe disability in childhood.
4. Ventilation for more than 24 hours.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (27 February 2012).

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

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved discrepancies through discussion or, if required, consulted a third assessor.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, consulted a third person. Data were entered into Review Manager software (RevMan 2011) 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 the included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (*Handbook*) (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

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

We described for the 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 assessed the method as:

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

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

We described for the included study the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

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

(3) Blinding (checking for possible performance bias)

We described for the included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies 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 have assessed the methods as:

- low risk, high risk or unclear risk for participants or personnel.
- low risk, high risk or unclear risk for outcome assessors.

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

We described for the 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:

- low risk (less than 5% of participants);
- high risk (5% or more of participants);
- unclear risk.

(5) Selective reporting bias

We described for the included study how we investigated the possibility of selective outcome reporting bias and what we found.
We assessed the methods as:

- low risk (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 (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.

(6) Other sources of bias

We described for the included study any important concerns we have about other possible sources of bias.
We assessed whether the included study was free of other problems that could put it at risk of bias:

- low risk;
- high risk;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether the included study was at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We considered this to be unlikely and therefore have not undertaken sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

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. We only identified one study for inclusion in this review. In future updates of this review, we will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials. However, in future updates of this review we will include cluster-randomised trials in the analyses if they are identified, along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are

used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise 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 randomisation unit is considered to be unlikely.

We will also acknowledged heterogeneity in the randomisation unit and perform a separate meta-analysis.

Dealing with missing data

For the included study, we noted levels of attrition. If in future updates of this review, we identify studies with high levels of missing data (5% or more of participants), we will explore the impact of including them in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes we have carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we have attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial is the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

Only one study was identified by our search strategy. However, if other studies are identified in future updates of this review, we will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if T^2 is greater than zero and either I^2 is greater than 30% or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of this review, 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, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If we detect asymmetry in any of these tests or by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). In future updates of this review, 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. We will treat the random-effects summary as the average range of possible treatment effects and discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combined trials.

If, in future updates of this review, if we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify more than one study in future updates of this review, and there is 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 planned to carry out the following subgroup analyses.

1. Gestation less than 28 weeks, 28 to 31+6 weeks, 32 to 36 weeks.
2. Singleton and multiple pregnancies.
3. Male and female babies.
4. Underlying cause of fetal compromise: placental insufficiency, congenital abnormality, isoimmunisation, intrauterine infection.
5. Severity of fetal compromise: positive end diastolic flow in umbilical artery Doppler, absent or reversed end-diastolic flow in umbilical artery Doppler, abnormal arterial or venous Doppler.

We planned to use the following outcomes in subgroup analysis.

1. Perinatal mortality.
2. Serious neonatal morbidity (composite outcome including bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), hypoxic ischaemic encephalopathy (HIE)).
3. Death or disability at or after two years of age.

Data were not available to allow us to perform any of the prespecified subgroup analyses, but these will be included in future updates of the review if other studies are identified. For fixed-effect inverse variance meta-analyses, we will examine differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

In the single study included in this review, data were reported for the following subgroups.

- Group A. Gestation 24 to 30 weeks.

- Group B. Gestation 31 to 36 weeks.

As the effect of gestation could be important, we performed *post hoc* subgroup analysis for these groups for the following outcome.

1. Death or disability at or after two or more years of age.

Data were not available to allow subgroup analysis of the other primary outcomes (extended perinatal mortality or serious neonatal morbidity).

Sensitivity analysis

In future updates of this review, as more data become available, we will perform sensitivity analyses to explore the effect of trial quality on results, if there is a risk of bias associated with the quality of some of the included trials. We will use sensitivity analysis to explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity and the effects of any assumptions made such as the value of the ICC used for cluster-randomised trials.

We will use the following outcomes in sensitivity analysis.

1. Perinatal mortality.
2. Serious neonatal morbidity (composite outcome including BPD, NEC, IVH, ROP, HIE).
3. Death or disability at or after two years of age.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

See Characteristics of included studies.

Results of the search

The search of the Pregnancy and Childbirth Group's Trials Register identified two trials (in six reports). One study has been included (Thornton 2004) and one excluded (Langenveld 2011).

Included studies

We included one study (Thornton 2004), involving 548 women (588 babies). The Growth Restriction Intervention Study (GRIT study), led to five publications (three manuscripts GRIT 2003; Thornton 2004; Walker 2011, and two abstracts Hornbuckle 1999; Schneider 2000).

Thornton 2004, compared outcomes of immediate delivery and deferred delivery in fetuses with suspected *in utero* compromise. It was a multicentre randomised trial recruiting over a seven-year period (November 1993 to March 2001), with participants recruited from 69 hospitals in 13 countries (Belgium, Cyprus, Czech Republic, Germany, Greece, Hungary, Italy, Netherlands, Poland, Portugal, Saudi Arabia, Slovenia, United Kingdom). Women were included if they were 24 to 36 weeks' gestation and had a pregnancy with suspected fetal compromise, with the umbilical Doppler waveform recorded, and clinical uncertainty as to whether the fetus should be immediately delivered or not. Immediate delivery was defined as delivery within 48 hours to allow completion of a steroid course to promote fetal lung maturity. Deferred delivery was when worsening test results or the passage of time favoured delivery, so safe delivery could be no longer deferred. The degree of fetal compromise was not specified, but data were collected to allow investigations of interactions between the degree of compromise and the gestation at randomisation, and outcome.

Women with both singleton (n = 509) and multiple (n = 39) pregnancies were included (588 babies). Both groups were comparable at randomisation. The primary outcome was originally "infant survival to hospital discharge and the Griffith's developmental quotient (DQ) at two years of age". However, this was changed to "death or disability at or after two years of age" which was felt to be a more precise outcome. Agreement for this change was obtained during the trial, from the data monitoring and ethics committee. Disability was defined as cerebral palsy, little or no vision, requirement for a hearing aid, or a Griffiths DQ of 70 or less. The primary outcome was reported in Thornton 2004. An earlier publication (GRIT 2003), reported early outcomes including mode of delivery, perinatal mortality and indicators of neonatal morbidity. A subsequent manuscript reported childhood outcomes (Walker 2011), including Kaufman-Assessment Battery for Children Mental Processing Component (Kaufman ABC MPC) and death or disability, at six to 13 years, in a subset of the original cohort. Two abstracts were also published (Hornbuckle 1999; Schneider 2000), but these were interim analysis and so data from these were not included in this review.

The study analysis and data monitoring were Bayesian. Odds ratios were calculated and used to revise hypothetical prior beliefs about the outcomes of immediate or deferred delivery. There were no specified stopping rules for the trial. Interim analyses of unmasked data were presented to the data monitoring committee every year and to clinical collaborators every two years. The aim of this was to allow individuals with strong prior beliefs on the value of intervention to stop recruiting if they were no longer clinically uncertain, and to encourage other clinicians to recruit if they became unsure of the benefit of delivery.

Excluded studies

The HYPITAT II trial (Langenveld 2011) is ongoing and is anticipated to complete in 2013. This study investigates immediate or deferred delivery for maternal indications (gestational hypertension, chronic hypertension or pre-eclampsia) rather than for

suspected fetal compromise.

Risk of bias in included studies

Allocation

In the included study (Thornton 2004), allocation was performed by an independent programmer. During office hours, a computer-generated sequence was used, and out of office hours, a paper-based number sequence with balanced blocks of eight to 12 was used, so allocation was masked from participating clinicians.

Blinding

The nature of the intervention meant that blinding of patients or personnel was not possible. Indeed, unmasked interim analysis data were presented to collaborators, as part of trial design, as analysis was planned to be Bayesian with odds ratios obtained used to revise prior beliefs about outcomes.

Assesors performing assessments at two years were blinded to randomisation group so the risk of detection bias was low for the primary outcome.

Incomplete outcome data

Two-hundred and ninety-six fetuses were randomised to immediate delivery, and 291 fetuses to deferred delivery. One woman with a singleton pregnancy randomised to deferred delivery discharged herself from hospital and was lost to follow-up. Early outcomes of all other fetuses are reported (GRIT 2003), thus for early outcomes there was less than 5% incomplete data and the risk of bias is low.

At two-year assessment, an additional six babies in the immediate delivery group and eight in the deferred group were lost to follow-up (Thornton 2004), thus for two-year outcomes there was less than 5% incomplete data and the risk of bias is low.

Childhood follow-up was attempted in children born to women randomised in five of the original recruiting countries (Germany, Italy, The Netherlands, Slovenia, and United Kingdom; Walker 2011). Data from Italy were not reported due to a high loss to follow-up rate (75%). Follow-up data on children from other countries were available in 153/173 cases in the immediate delivery group and 149/ 183 in the deferred delivery group. As there is more than 5% incomplete data the risk of bias for childhood outcomes is high.

Selective reporting

The study protocol was published online and available for review. Outcomes and analysis strategies were prespecified, and there is no evidence of selective reporting of outcomes.

Other potential sources of bias

Multiple pregnancies were included, but no adjustment was made in the analysis to take account of non-independence between babies from the same pregnancy (Brocklehurst 2004).

Effects of interventions

Primary outcomes

There was no difference in perinatal mortality with immediate delivery compared to deferred delivery (risk ratio (RR) 1.17, 95% confidence interval (CI) 0.67 to 2.04, one trial, 587 participants (Analysis 1.1)). There was also no difference in risk of the composite outcome of death or disability at or after two years (RR 1.22, 95% CI 0.85 to 1.75, one trial, 573 participants (Analysis 1.2)). We were not able to calculate composite rates of severe neonatal morbidity, even though individual morbidities were reported, due to the risk of double counting infants with more than one morbidity.

Secondary outcomes

There was a trend for decreased stillbirth with immediate delivery (RR 0.22, 95% CI 0.05 to 1.00, one trial, 587 participants (Analysis 1.3)). However, this was offset by a trend for increased neonatal mortality (RR 1.84, 95% CI 0.93 to 3.62, one trial, 576 participants (Analysis 1.4)). There were no differences in post neonatal mortality (RR 0.66, 95% CI 0.19 to 2.33, one trial, 541 participants (Analysis 1.5)) with immediate delivery compared to deferred delivery.

There were no differences between the immediate delivery and deferred delivery groups in any neonatal morbidity or marker of neonatal morbidity prespecified in the protocol. Data were available on cord pH less than 7.00 (RR 0.50, 95% CI 0.09 to 2.70, one trial, 400 participants (Analysis 1.7)); Apgar less than seven at five minutes (RR 1.49, 95% CI 0.82 to 2.70, one trial, 560 participants (Analysis 1.8)); convulsions (RR 1.44, 95% CI 0.24 to 8.55, one trial, 576 participants (Analysis 1.10)); IVH or GMH (RR 1.28, 95% CI 0.84 to 1.95, one trial, 576 participants (Analysis 1.11)); necrotising enterocolitis (RR 1.44, 95% CI 0.71 to 2.93, one trial, 576 participants (Analysis 1.12)); and PVL or ventriculomegaly (RR 2.04, 95% CI 0.89 to 4.65, one trial, 576 participants (Analysis 1.13)).

More children in the immediate delivery group had cerebral palsy at or after two years of age (RR 5.88, 95% CI 1.33 to 26.02, one trial, 507 participants (Analysis 1.15)). There was, however, no difference in neurodevelopment impairment at or after two years (RR 1.72, 95% CI 0.86 to 3.41, one trial, 507 participants (Analysis 1.14)).

Non-prespecified outcomes

More babies in the immediate delivery group were ventilated for more than 24 hours (RR 1.54, 95% CI 1.20 to 1.97, one trial, 576 participants (Analysis 1.9)). There were no differences between the immediate delivery and deferred delivery groups in death at or after two years (RR 1.04, 95% CI 0.66 to 1.63, one trial, 573 participants (Analysis 1.6)); death or disability in childhood (six to 13 years of age) (RR 0.82, 95% CI 0.48 to 1.40, one trial, 302 participants (Analysis 1.16)); or mean difference (MD) in childhood Kaufman-ABC MPC Score (MD -1.00, 95% CI -4.47 to 2.47, one trial, 269 participants (Analysis 1.17)).

Subgroup analysis

Compared to deferred delivery, the RR of death or disability at two years with immediate delivery was 1.21 (95% CI 0.81 to 1.80) at 24 to 30 weeks (subgroup A), and 1.04 (95% CI 0.54 to 2.01) at 31 to 36 weeks (subgroup B). No significant difference in effect was found between the subgroups (P = 0.70) (*see* Analysis 1.19).

Maternal outcomes

More women in the immediate delivery group had caesarean delivery than in the deferred delivery group (RR 1.15, 95% CI 1.07 to 1.24, one trial, 547 participants (Analysis 1.18)). Data were not available on any other maternal outcomes.

DISCUSSION

Summary of main results

We identified one study (involving 548 women (588 babies)) examining whether immediate or deferred delivery improved outcomes when there is suspected fetal compromise in the preterm fetus. This study only included cases of suspected fetal compromise where there was uncertainty whether immediate delivery was indicated, thus results must be interpreted with caution. The available data showed immediate delivery results in higher rates of caesarean delivery than deferred delivery. Although no differences were evident in perinatal mortality or a composite measure of mortality and significant morbidity at two years, immediate delivery resulted in more neonatal ventilation and more cerebral palsy at two years of age. Childhood outcomes have also been reported, and although it must be noted that follow-up data were incomplete, no differences in outcome were found between immediate and deferred delivery groups. Together these findings suggest that where there is uncertainty whether or not to deliver a preterm fetus with suspected fetal compromise, there is no benefit to immediate delivery. Deferring delivery until test results worsen or increasing gestation favours delivery, may improve outcome for mother and neonate.

Overall completeness and applicability of evidence

There is a lack of trials in this area, and only one study was identified. Although it is a relatively large study, it has insufficient power to detect differences in neonatal mortality. It did not report any maternal outcomes, other than mode of delivery, or evaluate maternal satisfaction or economic outcomes.

The applicability of the findings is limited by several factors. Firstly, the broad inclusion criteria of the included trial, which recruited women with a range of different Doppler findings and obstetric complications, as well as different gestational ages. Numbers were insufficient to allow meaningful assessment of the impact of the severity of Doppler abnormality or the presence of obstetric conditions (for example, maternal hypertension or vaginal bleeding) on outcomes. The potential benefits of immediate delivery are likely to change with gestation. *Post hoc* subgroup analysis did not detect any significant difference in the effect of immediate or deferred delivery at early (24 to 30 weeks) or later (31 to 36 weeks) gestations, although there was a trend for an increased relative risk of death and disability at two years in the earlier gestation subgroup. Secondly, the study only included cases where the responsible clinician was uncertain whether to deliver or not. The authors were unable to report how many eligible women were offered participation, how many declined randomisation or how many potential participants were not included because of clinician certainty regarding timing for delivery. Thus, the proportion of pregnant women with suspected fetal compromise included in the study, and the generalisability of the findings, are unclear.

Thirdly, the difference in the median time between randomisation and delivery in the two groups was four days. The potential benefits of deferring delivery for longer or shorter periods cannot be presumed.

Finally, the study did not evaluate the use of more recently developed Doppler assessment techniques such as ductus venosus or middle cerebral artery waveforms which may diagnose more accurately severe compromise and help make decisions about the timing of delivery (Alfirevic 2010).

Quality of the evidence

We identified a single study, which was a large study of good quality, performed in 13 countries. The nature of the intervention means that participants could be blinded to treatment group. However, the assessors were blinded to allocation at two-year assessment.

The design and analysis of the included study was Bayesian. This differs from conventional methodology, where differences in out-

come are assessed with P values. Instead odds ratios were presented with credibility indices (similar to confidence intervals, representing the range in which the true value is likely to lie) and these were used to revise hypothetical prior beliefs that clinicians may have had regarding the benefits of immediate or deferred delivery. A purported advantage of this design is to allow assessment of the impact that the trial findings will have on clinical practice. Integral to the design is the presentation of unmasked data to collaborators as well as the data monitoring committee, in order to allow collaborators to modify their beliefs on the benefit or harm of the intervention. Although this differs from traditional methodology where interim analysis and findings are masked, we do not believe it was an important bias.

Despite the robustness of the study design of the included trial, the lack of other studies and limited applicability of the findings mean caution must be used in the interpretation of the findings.

Potential biases in the review process

We specified broad inclusion criteria for this review, so we could use all the available evidence. However, only one study was identified despite a rigorous literature search, meaning analysis was limited.

Agreements and disagreements with other studies or reviews

We are not aware of any other studies or reviews investigating this question. The results of the Truffle Study are awaited (Protocol 02PRT/34 *Trial of umbilical and fetal flow in Europe (TRUFFLE)*: a multicentre randomised study), which aims to investigate which method of assessment (venous Doppler or cardiotocograph) should be used to determine timing of delivery of the preterm fetus with suspected fetal compromise.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there is insufficient evidence on the benefits and harms of immediate delivery compared with deferred delivery in cases of suspected fetal compromise at preterm gestations to make firm recommendations to guide clinical practice. However, immediate delivery appears to increase caesarean delivery and does not improve neonatal outcome. When there is uncertainty regarding the optimal time for delivery of the preterm fetus with suspected fetal compromise, deferring delivery until test results worsen or increasing gestation favours delivery, may improve outcome for mother and neonate.

Implications for research

Further randomised trials are required. These should be adequately powered to detect differences in maternal and neonatal morbidity and mortality. Such studies should include economic evaluation and investigation of maternal preferences.

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As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Thornton 2004

Methods	Randomised controlled trial.
Participants	548 women (singleton 509, multiple 39) 588 babies, 24-36 weeks' gestation with umbilical artery Doppler recorded and uncertainty whether to deliver or not Outcomes available at or after 2 years for 575 babies.
Interventions	Immediate delivery (allowing 48 hours for completion of steroids) OR deferred delivery (when safe delivery could be delayed no longer, because worsening test results or the passage of time favoured delivery)
Outcomes	Death or disability (cerebral palsy, little or no vision, requirement for a hearing aid, or a Griffiths DQ of 70 or less) at or after 2 years of age
Notes	Primary outcome of GRIT trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence.
Allocation concealment (selection bias)	Low risk	Allocation by an independent programmer.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to allocation at 2 year follow-up. It is unclear whether assessors were blinded to allocation at childhood follow-up therefore unclear risk of bias for these outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% incomplete data for early and 2 year outcomes. More than 5% missing data for childhood outcomes, therefore high risk of bias for these outcomes
Selective reporting (reporting bias)	Low risk	Protocol published and no suggestion of selective reporting of outcomes
Other bias	High risk	Trial did not account for non-independence of data in relation to twin pregnancies

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

Study	Reason for exclusion
Langenveld 2011	Protocol for ongoing trial (anticipated to complete in 2013) investigating immediate or deferred delivery for maternal indications (gestational hypertension, chronic hypertension or pre-eclampsia)

DATA AND ANALYSES

Comparison 1. Immediate delivery versus deferred delivery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Extended perinatal mortality	1	587	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.67, 2.04]
2 Death or disability at or after 2 years	1	573	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.85, 1.75]
3 Stillbirth	1	587	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 1.00]
4 Neonatal mortality	1	576	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.93, 3.62]
5 Postneonatal mortality (> 28 days to discharge)	1	541	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.19, 2.33]
6 Death at or after 2 years age	1	573	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.66, 1.63]
7 Cord pH less than 7.0	1	400	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.09, 2.70]
8 Apgar less than 7 at 5 minutes	1	560	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.82, 2.70]
9 Ventilation > 24 hours	1	576	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.20, 1.97]
10 Convulsions	1	576	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.24, 8.55]
11 Interventricular haemorrhage or germinal matrix haemorrhage	1	576	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.84, 1.95]
12 Necrotising enterocolitis	1	576	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.71, 2.93]
13 Periventricular leucomalacia or ventriculomegaly	1	576	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.89, 4.65]
14 Neurodevelopmental impairment at or after 2 years	1	507	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.86, 3.41]
15 Cerebral palsy at or after 2 years of age	1	507	Risk Ratio (M-H, Fixed, 95% CI)	5.88 [1.33, 26.02]
16 Death of severe disability 6-13 years	1	302	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.48, 1.40]
17 Kaufman-ABC MPC	1	269	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-4.47, 2.47]
18 Caesarean delivery	1	547	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.07, 1.24]
19 Subgroup analysis: death or disability at or after 2 years of age	1	573	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.82, 1.62]
19.1 24-30 weeks gestation	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.81, 1.80]
19.2 31-36 weeks	1	373	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.54, 2.01]

Analysis 1.1. Comparison 1 Immediate delivery versus deferred delivery, Outcome 1 Extended perinatal mortality.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 1 Extended perinatal mortality

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	25/296	21/291		100.0 %	1.17 [0.67, 2.04]
Total (95% CI)	**296**	**291**		**100.0 %**	**1.17 [0.67, 2.04]**

Total events: 25 (Immediate delivery), 21 (Deferred delivery)
Heterogeneity: not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Immediate delivery versus deferred delivery, Outcome 2 Death or disability at or after 2 years.

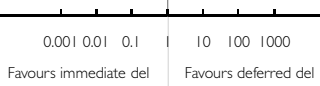
Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 2 Death or disability at or after 2 years

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	55/290	44/283		100.0 %	1.22 [0.85, 1.75]
Total (95% CI)	**290**	**283**		**100.0 %**	**1.22 [0.85, 1.75]**

Total events: 55 (Immediate delivery), 44 (Deferred delivery)
Heterogeneity: not applicable
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Immediate delivery versus deferred delivery, Outcome 3 Stillbirth.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 3 Stillbirth

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	2/296	9/291		100.0 %	0.22 [0.05, 1.00]
Total (95% CI)	**296**	**291**		**100.0 %**	**0.22 [0.05, 1.00]**
Total events: 2 (Immediate delivery), 9 (Deferred delivery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.96 (P = 0.050)					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 Immediate delivery versus deferred delivery, Outcome 4 Neonatal mortality.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 4 Neonatal mortality

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	23/294	12/282		100.0 %	1.84 [0.93, 3.62]
Total (95% CI)	**294**	**282**		**100.0 %**	**1.84 [0.93, 3.62]**
Total events: 23 (Immediate delivery), 12 (Deferred delivery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.76 (P = 0.079)					
Test for subgroup differences: Not applicable					

Analysis 1.5. Comparison 1 Immediate delivery versus deferred delivery, Outcome 5 Postneonatal mortality (> 28 days to discharge).

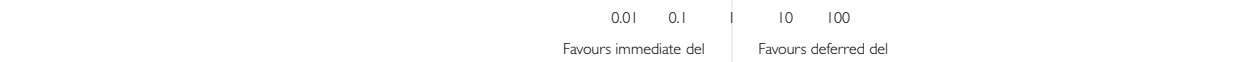
Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 5 Postneonatal mortality (> 28 days to discharge)

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	4/271	6/270		100.0 %	0.66 [0.19, 2.33]
Total (95% CI)	**271**	**270**		**100.0 %**	**0.66 [0.19, 2.33]**

Total events: 4 (Immediate delivery), 6 (Deferred delivery)
Heterogeneity: not applicable
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Immediate delivery versus deferred delivery, Outcome 6 Death at or after 2 years age.

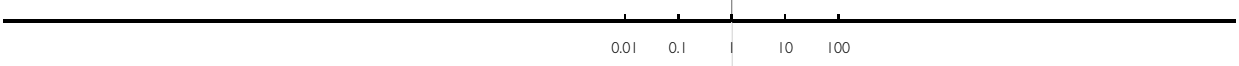
Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 6 Death at or after 2 years age

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	34/290	32/283		100.0 %	1.04 [0.66, 1.63]
Total (95% CI)	**290**	**283**		**100.0 %**	**1.04 [0.66, 1.63]**

Total events: 34 (Immediate delivery), 32 (Deferred delivery)
Heterogeneity: not applicable
Test for overall effect: Z = 0.16 (P = 0.88)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Immediate delivery versus deferred delivery, Outcome 7 Cord pH less than 7.0.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 7 Cord pH less than 7.0

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	2/200	4/200		100.0 %	0.50 [0.09, 2.70]
Total (95% CI)	**200**	**200**		**100.0 %**	**0.50 [0.09, 2.70]**

Total events: 2 (Immediate delivery), 4 (Deferred delivery)
Heterogeneity: not applicable
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Immediate delivery versus deferred delivery, Outcome 8 Apgar less than 7 at 5 minutes.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 8 Apgar less than 7 at 5 minutes

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	25/278	17/282		100.0 %	1.49 [0.82, 2.70]
Total (95% CI)	**278**	**282**		**100.0 %**	**1.49 [0.82, 2.70]**

Total events: 25 (Immediate delivery), 17 (Deferred delivery)
Heterogeneity: not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Immediate delivery versus deferred delivery, Outcome 9 Ventilation > 24 hours.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 9 Ventilation > 24 hours

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	114/294	71/282		100.0 %	1.54 [1.20, 1.97]
Total (95% CI)	**294**	**282**		**100.0 %**	**1.54 [1.20, 1.97]**

Total events: 114 (Immediate delivery), 71 (Deferred delivery)
Heterogeneity: not applicable
Test for overall effect: Z = 3.42 (P = 0.00062)
Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Immediate delivery versus deferred delivery, Outcome 10 Convulsions.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 10 Convulsions

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	3/294	2/282		100.0 %	1.44 [0.24, 8.55]
Total (95% CI)	**294**	**282**		**100.0 %**	**1.44 [0.24, 8.55]**

Total events: 3 (Immediate delivery), 2 (Deferred delivery)
Heterogeneity: not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Immediate delivery versus deferred delivery, Outcome 11 Interventricular haemorrhage or germinal matrix haemorrhage.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 11 Interventricular haemorrhage or germinal matrix haemorrhage

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	44/294	33/282		100.0 %	1.28 [0.84, 1.95]
Total (95% CI)	**294**	**282**		**100.0 %**	**1.28 [0.84, 1.95]**
Total events: 44 (Immediate delivery), 33 (Deferred delivery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					
Test for subgroup differences: Not applicable					

Analysis 1.12. Comparison 1 Immediate delivery versus deferred delivery, Outcome 12 Necrotising enterocolitis.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 12 Necrotising enterocolitis

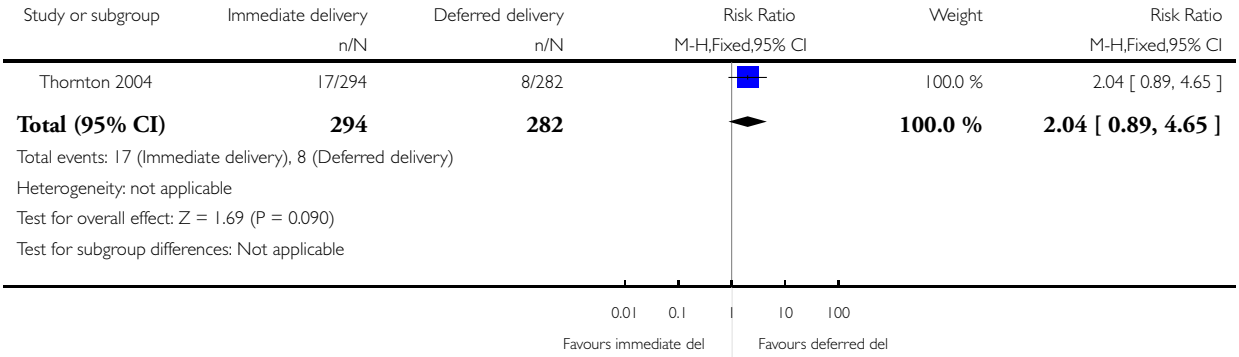
Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	18/294	12/282		100.0 %	1.44 [0.71, 2.93]
Total (95% CI)	**294**	**282**		**100.0 %**	**1.44 [0.71, 2.93]**
Total events: 18 (Immediate delivery), 12 (Deferred delivery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
Test for subgroup differences: Not applicable					

Analysis 1.13. Comparison 1 Immediate delivery versus deferred delivery, Outcome 13 Periventricular leucomalacia or ventriculomegaly.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 13 Periventricular leucomalacia or ventriculomegaly

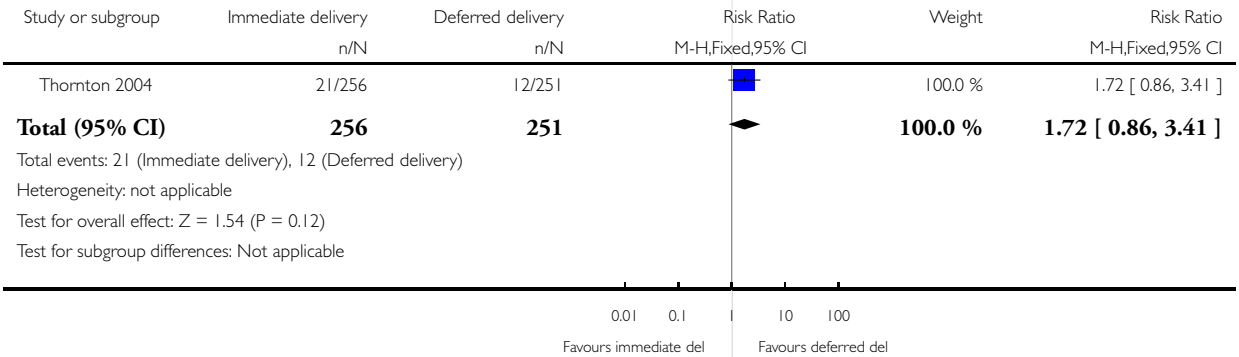


Analysis 1.14. Comparison 1 Immediate delivery versus deferred delivery, Outcome 14 Neurodevelopmental impairment at or after 2 years.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 14 Neurodevelopmental impairment at or after 2 years



Analysis 1.15. Comparison 1 Immediate delivery versus deferred delivery, Outcome 15 Cerebral palsy at or after 2 years of age.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 15 Cerebral palsy at or after 2 years of age

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	12/256	2/251		100.0 %	5.88 [1.33, 26.02]
Total (95% CI)	**256**	**251**		**100.0 %**	**5.88 [1.33, 26.02]**
Total events: 12 (Immediate delivery), 2 (Deferred delivery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.34 (P = 0.019)					
Test for subgroup differences: Not applicable					

Analysis 1.16. Comparison 1 Immediate delivery versus deferred delivery, Outcome 16 Death of severe disability 6-13 years.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 16 Death of severe disability 6-13 years

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	21/153	25/149		100.0 %	0.82 [0.48, 1.40]
Total (95% CI)	**153**	**149**		**100.0 %**	**0.82 [0.48, 1.40]**
Total events: 21 (Immediate delivery), 25 (Deferred delivery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					
Test for subgroup differences: Not applicable					

Analysis 1.17. Comparison 1 Immediate delivery versus deferred delivery, Outcome 17 Kaufman-ABC MPC.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 17 Kaufman-ABC MPC

Study or subgroup	Immediate delivery N	Mean(SD)	Deferred delivery N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Thornton 2004	139	95 (15)	130	96 (14)		100.0 %	-1.00 [-4.47, 2.47]
Total (95% CI)	**139**		**130**			**100.0 %**	**-1.00 [-4.47, 2.47]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.57 (P = 0.57)

Test for subgroup differences: Not applicable

Analysis 1.18. Comparison 1 Immediate delivery versus deferred delivery, Outcome 18 Caesarean delivery.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 18 Caesarean delivery

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thornton 2004	249/273	217/274		100.0 %	1.15 [1.07, 1.24]
Total (95% CI)	**273**	**274**		**100.0 %**	**1.15 [1.07, 1.24]**

Total events: 249 (Immediate delivery), 217 (Deferred delivery)

Heterogeneity: not applicable

Test for overall effect: Z = 3.90 (P = 0.000097)

Test for subgroup differences: Not applicable

Analysis 1.19. Comparison 1 Immediate delivery versus deferred delivery, Outcome 19 Subgroup analysis: death or disability at or after 2 years of age.

Review: Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes

Comparison: 1 Immediate delivery versus deferred delivery

Outcome: 19 Subgroup analysis: death or disability at or after 2 years of age

Study or subgroup	Immediate delivery n/N	Deferred delivery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24-30 weeks gestation					
Thornton 2004	39/107	28/93		65.6 %	1.21 [0.81, 1.80]
Subtotal (95% CI)	**107**	**93**		**65.6 %**	**1.21 [0.81, 1.80]**
Total events: 39 (Immediate delivery), 28 (Deferred delivery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.94 (P = 0.35)					
2 31-36 weeks					
Thornton 2004	16/183	16/190		34.4 %	1.04 [0.54, 2.01]
Subtotal (95% CI)	**183**	**190**		**34.4 %**	**1.04 [0.54, 2.01]**
Total events: 16 (Immediate delivery), 16 (Deferred delivery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.91)					
Total (95% CI)	**290**	**283**		**100.0 %**	**1.15 [0.82, 1.62]**
Total events: 55 (Immediate delivery), 44 (Deferred delivery)					
Heterogeneity: Chi^2 = 0.15, df = 1 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%					

HISTORY

Protocol first published: Issue 2, 2011

Review first published: Issue 7, 2012

CONTRIBUTIONS OF AUTHORS

Sarah Stock is guarantor for the review. All authors contributed to design of this protocol.

DECLARATIONS OF INTEREST

Sarah Stock - None known.

Jane Norman has received a grant to examine the effect of induction of labour for prevention of neonatal mortality. She has many other research grants for studies to improve perinatal outcome, some in preterm infants, but none directly related to the question of this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The Methods section has been updated.

The definition of the primary outcome perinatal mortality (intrauterine death or death in the first seven days of life) was amended to represent extended perinatal mortality (intrauterine death or death in the first 28 days of life), as deaths in the neonatal period are frequently secondary to obstetric causes, and these were felt to be relevant.

We also reported the following non-prespecified outcomes that we considered to be important: death at or after two years of age; Kaufman-Assessment Battery for Children Mental Processing Component Score in childhood; death or severe disability in childhood; ventilation for more than 24 hours.

We had intended to perform subgroup analyses for gestations less than 28 weeks, 28 to 31+6 weeks and 32 to 36 weeks. Data were not available for the groups specified but were available for gestations 24 to 30 weeks and gestations 31 to 36 weeks. As the effect of gestation could be important, we performed *post hoc* subgroup analysis for these groups.

INDEX TERMS

Medical Subject Headings (MeSH)

*Fetal Distress [complications]; *Infant, Premature; Cerebral Palsy [etiology]; Cesarean Section [utilization]; Delivery, Obstetric [adverse effects; *methods]; Infant Mortality; Infant, Newborn; Randomized Controlled Trials as Topic; Respiration, Artificial [utilization]; Watchful Waiting

MeSH check words

Female; Humans; Infant; Pregnancy