Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation (Review)

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TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 2
OBJECTIVES . . . 3
METHODS . . . 4
RESULTS . . . 8
Figure 1. . . . 9
Figure 2. . . . 10
DISCUSSION . . . 12
AUTHORS' CONCLUSIONS . . . 13
ACKNOWLEDGEMENTS . . . 13
REFERENCES . . . 13
CHARACTERISTICS OF STUDIES . . . 15
DATA AND ANALYSES . . . 23
Analysis 1.1. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 1 Eclampsia. . . . 24
Analysis 1.2. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 2 HELLP syndrome. . . . 24
Analysis 1.3. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 3 Pulmonary oedema. . . . 25
Analysis 1.4. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 4 Death of the baby (all stillbirths, neonatal and infant deaths). . . . 25
Analysis 1.5. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 5 Death of the baby (subgrouped by time of death). . . . 26
Analysis 1.6. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 6 Intraventricular haemorrhage or hypoxic ischaemic encephalopathy. . . . 27
Analysis 1.7. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 7 Renal failure. . . . 28
Analysis 1.8. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 8 Caesarean section. . . . 28
Analysis 1.9. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 9 Placental abruption. . . . 29
Analysis 1.10. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 10 Low Apgar score at five minutes (< 7 at five minutes). . . . 30
Analysis 1.11. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 11 Neonatal seizures. . . . 30
Analysis 1.12. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 12 Hyaline membrane disease. . . . 31
Analysis 1.13. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 13 Necrotising enterocolitis. . . . 32
Analysis 1.14. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 14 Baby ventilated. . . . 33
Analysis 1.15. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 15 Measures of long-term growth & development (cerebral palsy). . . . 33
Analysis 1.16. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 16 Measures of long-term growth & development (poor hearing/hearing aid). . . . 34
Analysis 1.17. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 17 Measures of long-term growth & development (impaired vision). . . . 35
Analysis 1.18. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 18 Small-for-gestational age. . . . 35

Analysis 1.19. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 19 Gestation at birth (days). 36
Analysis 1.20. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 20 Length of stay in neonatal intensive care unit (days). 37
Analysis 1.21. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 21 Admission to neonatal intensive care unit. 37
APPENDICES 38
WHAT'S NEW 39
HISTORY 39
CONTRIBUTIONS OF AUTHORS 39
DECLARATIONS OF INTEREST 40
SOURCES OF SUPPORT 40
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 40
INDEX TERMS 40

[Intervention Review]

Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

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ABSTRACT

Background

Severe pre-eclampsia can cause significant mortality and morbidity for both mother and child, particularly when it occurs remote from term, between 24 and 34 weeks' gestation. The only known cure for this disease is delivery. Some obstetricians advocate early delivery to ensure that the development of serious maternal complications, such as eclampsia (fits) and kidney failure are prevented. Others prefer a more expectant approach delaying delivery in an attempt to reduce the mortality and morbidity for the child associated with being born too early.

Objectives

The objective of the review was to compare the effects of a policy of interventionist care and early delivery with a policy of expectant care and delayed delivery for women with early onset severe pre-eclampsia.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (28 February 2013).

Selection criteria

Randomised trials comparing the two intervention strategies for women with early onset severe pre-eclampsia.

Data collection and analysis

Two review authors independently assessed trials for inclusion, extracted data and assessed risk of bias. Data were checked for accuracy.

Main results

Four trials, with a total of 425 women are included in this review. Trials were at low risk of bias for methods of randomisation and allocation concealment; high risk for blinding; unclear risk for incomplete outcome data and other bias; and low risk for selective reporting. There are insufficient data for reliable conclusions about the comparative effects on most outcomes for the mother. For the

baby, there is insufficient evidence for reliable conclusions about the effects on stillbirth or death after delivery (risk ratio (RR) 1.08, 95% confidence interval (CI) 0.69 to 1.71; four studies; 425 women). Babies whose mothers had been allocated to the interventionist group had more intraventricular haemorrhage (RR 1.82, 95% CI 1.06 to 3.14; one study; 262 women), more hyaline membrane disease (RR 2.30, 95% CI 1.39 to 3.81; two studies; 133 women), require more ventilation (RR 1.50, 95% CI 1.11 to 2.02; two studies; 300 women) and were more likely to have a lower gestation at birth in days (average mean difference (MD) -9.91, 95% CI -16.37 to -3.45; four studies; 425 women), more likely to be admitted to neonatal intensive care (RR 1.35, 95% CI 1.16 to 1.58) and have a longer stay in the neonatal intensive care unit (average MD 11.14 days, 95% CI 1.57 to 20.72 days; two studies; 125 women) than those allocated an expectant policy. Nevertheless, babies allocated to the interventionist policy were less likely to be small-for-gestational age (RR 0.30, 95% CI 0.14 to 0.65; two studies; 125 women). Women who had been allocated to the interventionist group were more likely to have a caesarean section (RR 1.09, 95% CI 1.01 to 1.18; four studies; 425 women) than those allocated an expectant policy. There were no statistically significant differences between the two strategies for any other outcomes.

Authors' conclusions

This review suggests that an expectant approach to the management of women with severe early onset pre-eclampsia may be associated with decreased morbidity for the baby. However, this evidence is based on data from only four trials. Further large trials are needed to confirm or refute these findings and establish if this approach is safe for the mother.

PLAIN LANGUAGE SUMMARY

Interventionist versus expectant care for severe pre-eclampsia before term

Women who develop pre-eclampsia (high blood pressure and protein in the urine) before 34 weeks of pregnancy (early onset) are at risk of severe complications, and even death. These involve the woman's liver, kidneys, clotting system and cause neurological disturbances such as headache, visual disturbances, and exaggerated tendon reflexes. If the placenta is involved, this can cause growth restriction or reduced amniotic fluid, placing the baby at risk. The only known cure for pre-eclampsia is delivery of the baby. Being born too early can in itself have problems for the baby, even with the administration of corticosteroids 24 to 48 hours beforehand to help mature the lungs. Some hospitals follow a policy of early delivery within 24 to 48 hours, interventionist management, whilst others prefer to delay delivery until it is no longer possible to safely stabilise the woman's condition, expectant management.

This review included four trials that randomly assigned women to a policy of interventionist management or expectant management when presenting with severe pre-eclampsia before 34 weeks of pregnancy. A total of 425 women were included in these four trials. Babies born to women allocated to an interventionist approach were more likely to experience adverse effects such as intraventricular haemorrhage and neonatal respiratory distress syndrome. They were also more likely to require admission to the neonatal intensive care unit and ventilation, have a longer stay in the neonatal unit and weigh less at birth than those babies born to women allocated to an expectant management approach. Women in the interventionist group were also more likely to require caesarean section for delivery. Delaying delivery may therefore be more beneficial for the baby. There are insufficient data, however, for reliable conclusions about the comparative effects on most outcomes for the mother and hence the maternal safety of an expectant approach.

This evidence is based on data from only four small trials. Further large trials with long-term follow-up of the children are needed to confirm or refute whether expectant care is better than early delivery for women who suffer from severe pre-eclampsia before 34 weeks of pregnancy.

BACKGROUND

Pre-eclampsia is a multisystem disorder that is usually associated with raised blood pressure and proteinuria, but can also involve the woman's liver, kidneys, clotting system, or brain. If the placenta is involved this may lead to growth restriction or premature birth. Pre-eclampsia is a relatively common complication of pregnancy, and can occur at any time during the second half of pregnancy or in the first few weeks after delivery. Prediction models for adverse

maternal outcome have been developed and validated in recent times (von Dadelszen 2011), but there is still a paucity of data to guide the clinician on the timing of delivery to ensure safety of both the mother and the baby in the long term. Pre-eclampsia is described in more detail in the generic protocol on interventions for treatment of pre-eclampsia and its consequences (Duley 2009).

Description of the condition

Hypertension in pregnancy is defined as a systolic blood pressure of 140 mmHg or more, and/or a diastolic pressure of 90 mmHg or more. To be diagnosed with pre-eclampsia the hypertension has to arise de novo after 20 weeks of pregnancy in combination with proteinuria defined as greater than 300 mg of total protein in a 24-hour urine collection (Davey 1988). Recently, proteinuria has been assessed using a spot urine measuring the protein to creatinine ratio. A protein: creatinine ratio of 30 mg/mmol correlates with a 24-hour protein excretion of greater than 300 mg in 24 hours (Morris 2012). This method of estimating the amount of protein being excreted has several advantages over the 24-hour urine collection and has been endorsed in a Royal College of Obstetricians and Gynaecologists (RCOG) Pre-eclampsia study group consensus statement (RCOG 2003). However, pre-eclampsia is a multisystem disorder and the diagnosis of hypertension and proteinuria is considered to be too restrictive for clinical practice. Clinicians are all too aware that the disease can present in several ways and it is necessary to be vigilant when assessing women with symptoms and signs that are strongly associated with the disease. This has led to a widening of the definition for clinical purposes, to include the following: de novo hypertension after 20 weeks' gestation and new onset of one of the following: a) proteinuria as defined above; b) renal insufficiency (creatinine $\geq$ 0.09 mmol/L, or oliguria; c) liver disease (raised transaminases and/or severe right upper quadrant or epigastric pain); d) neurological problems, convulsions (eclampsia), hyper-reflexia with clonus (involuntary muscular contractions), severe headaches, persistent visual disturbances (scotoma); e) haematological disturbances: thrombocytopenia (reduced numbers of platelets), disseminated intravascular coagulation, haemolysis; or f) fetal growth restriction (Brown 2001).
There is no widely accepted definition of severe pre-eclampsia (Duley 2009). Nevertheless, the features described above in combination with the early onset of the disease between 24 and 34 weeks' gestation, would be considered by most clinicians to represent severe pre-eclampsia. We therefore did not further define nor categorise "severity".

Description of the intervention

Within clinical practice, some units advocate early delivery, which has been referred to as 'aggressive management' (Sibai 1984), but in this review the term 'interventionist' is preferred. This means delivery by either induction of labour or caesarean section after corticosteroids have been given to improve fetal lung maturation, which in practice is after 24 to 48 hours (Crowley 1996). Others prefer to give corticosteroids, stabilise the woman's condition and then, if possible, aim to delay delivery. This is usually known as 'expectant management' (Derham 1989). The greatest dilemma in when to deliver is balancing the risks to mother and baby when the pregnancy is somewhere between 24 to 34 weeks. Early delivery resulting in a very premature baby could lead to more neonatal complications such as respiratory distress syndrome (difficulty in breathing and oxygenation), intraventricular haemorrhage (bleeding into the cavities of the brain) and necrotising enterocolitis (bleeding into the wall of the bowel due to a lack of oxygen). Conversely, delaying delivery in an attempt to allow fetal maturation could place the mother in jeopardy and at risk of multisystem organ failure as outlined above. It also prolongs the time that a fetus is in a potentially hostile in utero environment. This in turn will continue to adversely affect the growth of the fetus and may result in an intrauterine death, from severe hypoxia or an acute event such as an abruption. Although the precise cut offs for gestational age will vary with different settings, before 24 weeks the child has little chance of survival. After 34 weeks the prognosis improves with nearly 100 per cent survival. Between 24 and 34 weeks mortality decreases with increasing gestational age, but especially below 28 weeks there is also considerable risk of survival with severe disability. A structured review of observational studies found that expectant care for severe pre-eclampsia was associated with a prolongation of the pregnancy by between one and two weeks with better outcomes for babies and low risks for the mother. There were fewer neonatal deaths and complications of prematurity (Magee 2009).

Why it is important to do this review

This difficult clinical dilemma occurs relatively frequently in large units, and currently decisions are based mainly upon personal experience rather than good evidence. There is a great need for reliable data to help inform this decision-making.
Other aspects of care for women with severe pre-eclampsia are dealt with in other reviews. These include drugs for lowering very high blood pressure (Duley 2006), prophylactic anticonvulsants (Duley 2010) and plasma volume expansion (Duley 1999b). Prevention of pre-eclampsia is covered by reviews of calcium supplementation (Hofmeyr 2010), antiplatelets (Duley 2007), salt intake (Duley 1999a; Duley 2005) and magnesium supplementation (Makrides 2001).

OBJECTIVES

To evaluate the comparative benefits and risks of a policy of early delivery by induction of labour or by caesarean section after suf-

ficient time has elapsed to administer corticosteroids, and allow them to take effect; with a policy of delaying delivery (expectant care) for women with severe pre-eclampsia between 24 and 34 weeks.

METHODS

Criteria for considering studies for this review

Types of studies

All adequately randomised trials comparing interventionist (aggressive) with expectant care (delayed delivery) for women with severe early onset pre-eclampsia. Quasi-random designs, such as alternate numbers or allocation by the day of the week, were excluded.

Types of participants

Women with severe pre-eclampsia before or equal to 34 weeks' gestation. Severe pre-eclampsia was defined as high blood pressure, $\geq$ 140/90 mmHg on two consecutive occasions four or more hours apart and proteinuria greater than 300 mg/24 hours. Alternatively as:

- severe hypertension (blood pressure at least 160 mmHg systolic, or 110 mmHg diastolic) alone;

or hypertension as defined above plus one or more of the following criteria:

- severe proteinuria (usually at least 3 g (range 2 g to 5 g) protein in 24 hours, or 3+ on dipstick);
- reduced urinary volume (less than 500 mL in 24 hours), upper abdominal pain, pulmonary oedema;
- neurological disturbances (such as headache, visual disturbances, and exaggerated tendon reflexes);
- impaired liver function tests, high serum creatinine, low platelets;
- suspected intrauterine growth restriction or reduced liquor volume.

This latter set of criteria reflect the natural history of the disease and clinical practice when diagnosing severe pre-eclampsia.

Types of interventions

Any comparison of a policy of early elective delivery by induction of labour or by caesarean section (interventionist management) with a policy of delayed delivery (expectant management). If corticosteroids were used within the trial, they should have been used for both types of care. As the beneficial effects of a course of corticosteroids are so important, any study where corticosteroids were only administered to one group but not the other was excluded.

Types of outcome measures

Primary outcomes

For the woman

- Death
- Eclampsia (fitting)
- Stroke (brain damage)
- HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome
- Pulmonary oedema (fluid in the lungs)

For the baby

- Stillbirth
- Neonatal death
- Intraventricular haemorrhage (bleeding in the brain) and/or hypoxic ischaemic encephalopathy

Secondary outcomes

For the woman

- Renal failure (kidney failure)
- Liver failure
- Cardiac arrest
- The need for invasive monitoring, such as central venous catheterisation (intravenous lines into the great veins around the heart)
- Caesarean section
- Placental abruption

For the baby

- Low Apgar score at five minutes
- Neonatal seizures
- Hyaline membrane disease (stiff lungs)
- Pneumothorax (air leaks from the lungs)
- Necrotising enterocolitis (bleeding into the bowel wall)
- Ventilation (any ventilation, duration of ventilation)
- Measures of long-term growth and development, such as important impairment and cerebral palsy
- Small-for-gestational age
- Gestation at birth

Use of health service resources

- Need for intensive care for the woman
- Need for high-dependency care or observation, or both, for the woman
- Length of stay in neonatal intensive care
- Admission to neonatal intensive care unit
- Surfactant for the baby
- Ventilation for the baby

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 (28 February 2013).

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.

For details of additional searching carried out in the previous version of the review, please see Appendix 1.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 2.

For this update we used the following methods when assessing the reports identified by the updated search. The two already included studies (Odendaal 1990; Sibai 1994) were also re-assessed using the following methods for 'Risk of bias' assessment.

Selection of studies

Two review authors (D Churchill (DC); L Jones (LJ)) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (DC; LJ) independently extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third author. We entered data into Review Manager software (RevMan 2012) and checked for accuracy. When information regarding any of the above was unclear, we contacted authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Disagreement was resolved by discussion or by involving a third author.

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

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

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

We described for each included study 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 would be unlikely to affect results. We planned to assess blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

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

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

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

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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

We 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 and 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 planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

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

(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:

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

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

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

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(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 *Cochrane 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 planned to explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios 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 planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods, if required.

Unit of analysis issues

Cluster-randomised trials

If we identify cluster-randomised trials in future updates, we will include them in the analyses along with individually-randomised

trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-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 acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are not a valid study design for this review.

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.

Assessment of heterogeneity

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

Assessment of reporting biases

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

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were 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 averaged treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the 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 T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

In future updates, if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.
We plan to carry out the following subgroup analyses based on:

1. gestation at trial entry: 24 to 28 weeks' gestation; 29 to 34 weeks' gestation; gestation mixed or unknown;
2. whether suspected intrauterine growth restriction at trial entry: suspected intrauterine growth restriction; no suspected intrauterine growth restriction; mixed or unknown.

The following primary outcomes will be used in subgroup analysis.

For the woman

- Death
- Eclampsia (fitting)
- Stroke (brain damage)
- HELLP syndrome
- Pulmonary oedema

For the baby

- Stillbirth
- Neonatal death
- Intraventricular haemorrhage

We will assess differences between subgroups using interaction tests available within (RevMan 2012).

Sensitivity analysis

In future updates, if more studies are identified and included in analyses, we plan to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result.

RESULTS

Description of studies

Results of the search

A total of seven trials were identified and four trials met our inclusion criteria (GRIT 2003; Mesbah 2003; Odendaal 1990; Sibai 1994) - *see* table of Characteristics of included studies.
Two trials were excluded (Gruppo di Studio1998; Langenveld 2011) - *see* table of Characteristics of excluded studies.
One trial is ongoing (Duvekot 2011) - *see* table of Ongoing studies.

Included studies

Four trials with a total of 425 women are included in this review.

Setting

One trial, was a UK based multi-centre trial involving 69 hospitals in 13 European countries (GRIT 2003). The other three trials were single-centre trials, based in Egypt (Mesbah 2003), South Africa (Odendaal 1990), and the USA (Sibai 1994).

Participants

In one trial, (GRIT 2003), 548 pregnant women with fetal growth restriction between 24 and 36 weeks' gestation, an umbilical artery Doppler waveform recorded and clinical uncertainty whether immediate delivery was indicated were examined. A subset of women from this trial (GRIT 2003) at less than or equal to 34 weeks' gestation (n = 262), who had severe pre-eclampsia were included in this review. Mesbah 2003 included 30 women with severe pre eclampsia between 28 and 33 weeks' gestation; Odendaal 1990 included 38 women with severe pre-eclampsia between 28 and 34 weeks' gestation; and Sibai 1994 included 95 women with severe pre-eclampsia at 28 to 32 weeks' gestation.

Interventions

In all trials, women had a 24- to 48-hour period of stabilisation during which they were given steroids to accelerate fetal lung maturity and if necessary magnesium sulphate to prevent seizures and antihypertensives to lower blood pressure. If they continued to meet the eligibility criteria at the end of this period they were then randomised. They were either randomised to the interventionist group, which involved immediate delivery by caesarean section or induction, or to the expectant management group, who were managed with hospitalisation and intensive maternal and fetal monitoring. Earlier delivery in this expectant group was implemented if either the maternal or fetal condition deteriorated, as determined by prespecified criteria.

Outcomes

The main outcomes in all studies included maternal, perinatal and neonatal morbidity and mortality outcomes. Only one trial included long-term outcomes (GRIT 2003): measures of long-term growth and development at two years.
For further details *see* Characteristics of included studies.

Excluded studies

Two trials were excluded as they did not meet the inclusion criteria of the review (Gruppo di Studio1998; Langenveld 2011). In both trials, the women did not have severe pre-eclampsia.
See table of Characteristics of excluded studies.

Risk of bias in included studies

The four trials were relatively small. Overall, two trials were judged to have a low risk of bias (GRIT 2003; Sibai 1994), one was unclear (Odendaal 1990) and one a high risk of bias (Mesbah 2003).
See Figure 1 and Figure 2 for summaries of 'Risk of bias' assessment.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

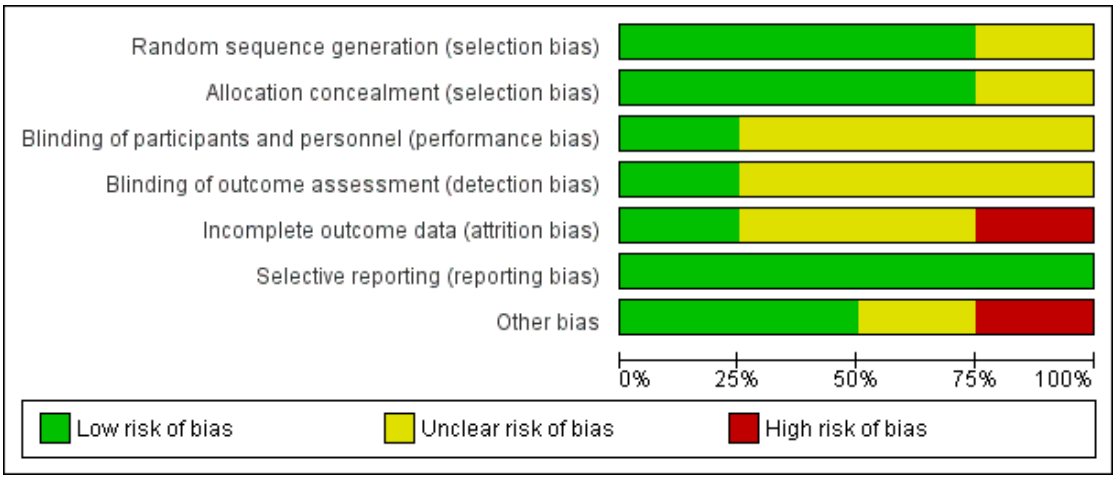
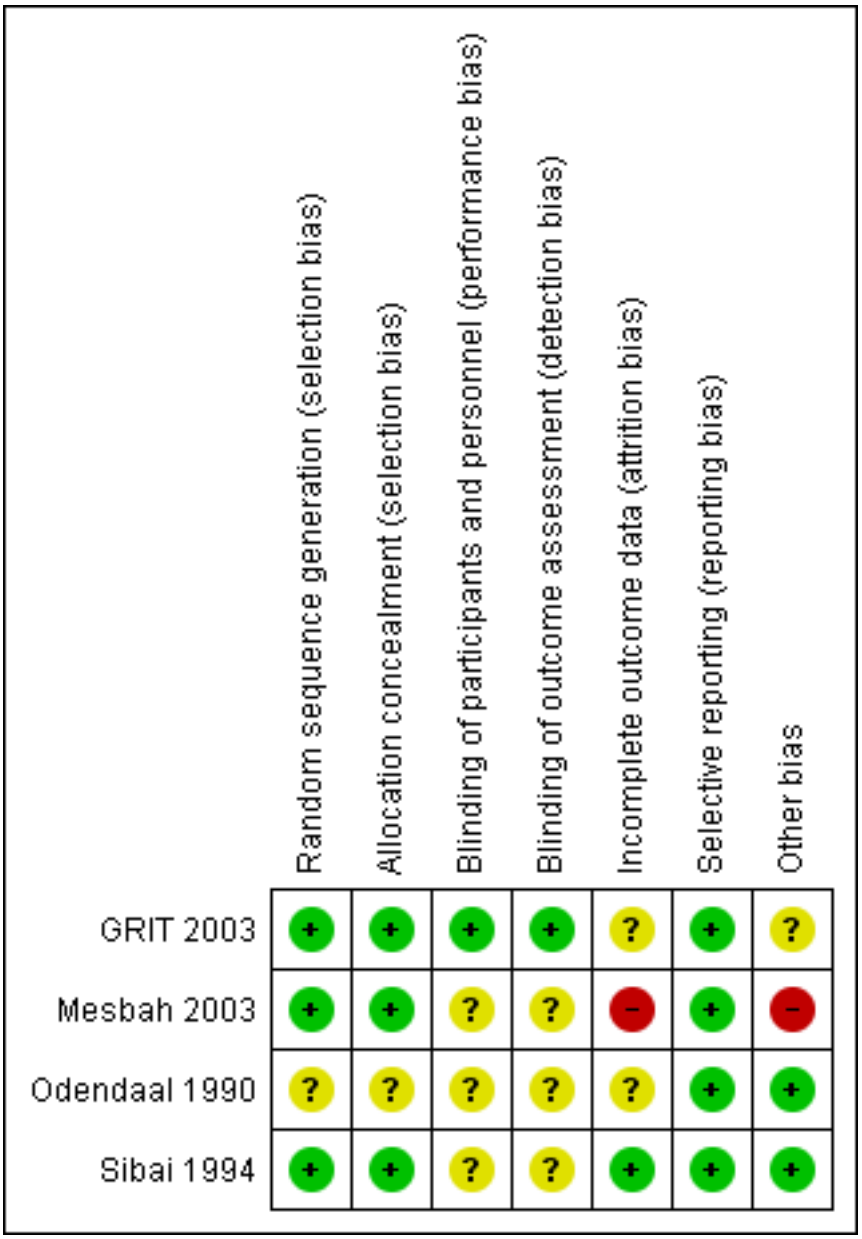


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

For one study, the method used for randomisation and concealment of allocation was not described (Odendaal 1990); in the other, three trials both methods of randomisation and concealment were adequate (GRIT 2003; Mesbah 2003; Sibai 1994).

Blinding

Blinding of participants, personnel or outcome assessors was not described in three of the trials (Mesbah 2003; Odendaal 1990; Sibai 1994). Blinding of outcome assessment for long-term outcomes such as Griffiths assessment was reported in one trial (GRIT 2003).

Incomplete outcome data

In one trial (Sibai 1994), all women appear to have been accounted for in the results. In one trial individual patient data for a subset of women with severe pre-eclampsia were provided by the authors of the original trial and it is not possible to tell how complete this data set is (GRIT 2003). In another trial, it is not clear from results tables how many were included in the analyses (Odendaal 1990). In one trial 41 women were recruited, but 11 (27%) were judged too compromised for expectant management and were delivered by caesarean section and after randomisation, five patients appear to be missing from the results table 2 (Mesbah 2003).

Selective reporting

All expected outcomes appear to have been reported upon in all four trials (GRIT 2003; Mesbah 2003; Odendaal 1990; Sibai 1994).

Other potential sources of bias

In two studies, baseline characteristics were similar between groups and no other sources of bias were apparent (Odendaal 1990; Sibai 1994). In one study, other bias may have been introduced as only a subset of the original randomised sample provided data for analysis, but this was not clear (GRIT 2003). In one study, the severe group were excluded from the study and no baseline characteristics described for this group of patients (Mesbah 2003).

Effects of interventions

1. Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Primary outcomes

Only one study (95 women) reported on primary outcomes of relevance to the woman. In this study there were no reports of eclampsia or pulmonary oedema in either group. There is insufficient evidence about the effects on HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome (one trial; 95 women; risk ratio (RR) 0.53; 95% confidence interval (CI) 0.05 to 5.68), Analysis 1.2. Death, stroke and pulmonary oedema were not reported in any of the trials.

For the baby, there is insufficient evidence for any reliable conclusions about the effects on stillbirth (four trials; 425 women; RR 0.20; 95% CI 0.03 to 1.16) or death after delivery (four trials; 425 women; RR 1.33; 95% CI 0.80 to 2.23), Analysis 1.5. Babies whose mothers had been allocated to the interventionist group had more intraventricular haemorrhage (one trial; 262 women; RR 1.82, 95% CI 1.06 to 3.14), Analysis 1.6.

Secondary outcomes

Women allocated to the interventionist group were more likely to have a caesarean section (four trials; 425 women; RR 1.09, 95% CI 1.01 to 1.18), Analysis 1.18, than those allocated an expectant policy. There were no statistically significant differences between the two management strategies for renal failure (two trials; 133 women; RR 0.30, 95% CI 0.01 to 6.97), Analysis 1.7, or placental abruption (two trials; 133 women; RR 0.80, 95% CI 0.26 to 2.40), Analysis 1.9. Liver failure, cardiac arrest and the need for invasive monitoring for the woman were not reported in any of the trials.

This review suggests that an interventionist policy of care may be associated with increased morbidity for the baby. For example, those babies whose mothers had been allocated to the interventionist group had more hyaline membrane disease (two trials; 133 women; RR 2.30, 95% CI 1.39 to 3.81), Analysis 1.12, were more likely to require ventilation (two trials; 300 women; RR 1.50, 95% CI 1.11 to 2.02), Analysis 1.14, and were more likely to have a lower gestation at birth (days) (four trials; 425 women; random-effects analysis; average mean difference (MD) -9.91, 95% CI -16.37 to -3.45; Heterogeneity: $Tau^2 = 31.74$; $I^2 = 76\%$), Analysis 1.19. Also, babies whose mothers had been allocated to the interventionist group were at increased risk of developing necrotising enterocolitis, (three trials; 395 women; RR 2.10, 95% CI 0.93 to 4.79), Analysis 1.13, although the results were not statistically significant, the confidence interval only just overlaps the line of no effect. This effect could be clarified by more data in future updates. Nevertheless, babies allocated to the interventionist policy were less likely to be small-for-gestational age (two trials; 125 women; RR 0.30, 95% CI 0.14 to 0.65), Analysis 1.18. There were no statistically significant differences between the two management

strategies for low Apgar score at five minutes, neonatal seizures, and measures of long-term growth and development, *see* Analysis 1.10; Analysis 1.11; Analysis 1.15; Analysis 1.16; Analysis 1.17. Babies whose mothers had been allocated to the interventionist group were more likely to be admitted to neonatal intensive care (two trials; 125 women; RR 1.35, 95% CI 1.16 to 1.58), Analysis 1.21, and have a longer stay in the neonatal intensive care unit (two trials; 125 women; random-effects analysis; average MD 11.14 days, 95% CI 1.57 to 20.72 days; Heterogeneity: $Tau^2 = 40.93$; $I^2 = 85\%$), Analysis 1.20, than those allocated an expectant policy. Other outcomes on use of health service resources were not reported in any of the trials (need for intensive care for the woman; need for high-dependency care or observation, or both, for the woman; surfactant for the baby).

DISCUSSION

Timing the delivery of a very premature infant in the presence of severe pre-eclampsia is a difficult clinical decision. When the mother's life is in danger there is no doubt that delivery is the only correct course of action. This situation is rare. More usually, the risks of maternal morbidity or intrauterine fetal demise, if the pregnancy is continued, have to be constantly balanced against the hazards of prematurity to the fetus if delivered. Most obstetricians would probably be cautious and expedite delivery in favour of the outcome for the mother and being able to guarantee a live baby at delivery. What is not clear is to what level this (if at all), adversely affects the baby.

Only the GRIT study pre-specified fetal assessment parameters as entry criteria into the study. The other studies used fetal assessment to trigger delivery if there was evidence of significant compromise. It is therefore not possible to compare the trials for the condition of the fetuses on trial entry. However it is unlikely that there would have been any clinical differences where this was not formally assessed at trial entry. If there were signs of imminent fetal demise then the women would not have been randomised into the trials. But there is the potential for unseen bias and future trials must include a formal assessment of fetal wellbeing on trial entry.

Currently there are insufficient data to justify any of our prespecified subgroup analyses. These will be included in future updates of this review, when larger trials become available.

It is not possible to draw firm conclusions from this review. However, the evidence is promising that short-term morbidity for the baby may be reduced by a policy of expectant care. This is perhaps surprising given that expectant management increases the length of time a fetus is within the hostile environment, with the potential to adversely affect fetal growth. In fact this is often stated as a reason for intervention. The results of this review suggest otherwise. While the babies in the expectant management group were smaller, their short-term outcomes were better. Before this policy can be recommended in clinical practice, further evidence is required to demonstrate that there is truly a short-term benefit for the baby and that it continues in the longer term. Reassurance is also needed to demonstrate that there is no increase in mortality for the child, or in morbidity for the mother.

Summary of main results

There is insufficient evidence for reliable conclusions about the effects of either management approach on stillbirth or death after delivery. However, there is some evidence from this review to suggest that a policy of delaying delivery reduces the morbidity experienced in the neonatal period of life. Fewer babies had intraventricular haemorrhages, hyaline membrane disease and reduced levels of ventilation in those allocated to expectant management. Babies in this group were also less likely to be admitted to the neonatal intensive care unit and when admitted stayed there for shorter periods of time. There were insufficient data to draw any conclusions about the effect a policy of expectant care had on the mothers health. None of the studies included had sufficient sample size to demonstrate differences in maternal outcome.

Overall completeness and applicability of evidence

There is insufficient evidence from this review to recommend a particular management policy for this area of obstetric care. The numbers of participants in the trials is too small to be able to demonstrate differences in most significant (primary) outcomes and where differences are found there is a considerable level heterogeneity or the contribution is from only one trial. The same is true for the analysis of the secondary outcome measures.

Quality of the evidence

Three of the trials included in the review were judged to be at unclear risk of both performance and detection bias. It is not possible to blind personnel and participants to interventions and most outcomes are objective outcomes, and are unlikely to be affected by blinding e.g. death, eclampsia. One study (Mesbah 2003), was in addition judged to be at risk of attrition bias. The GRIT 2003 trial was not originally designed to examine severe pre-eclampsia. It looked at interventionist versus expectant management for babies with growth restriction. A by-product of this study, was that a subset of women also had severe pre-eclampsia and it is these women who have been included in the review.

Potential biases in the review process

J Thornton was the Principle Investigator for the GRIT 2003 trial. To remove the potential for bias, the GRIT trial data were supplied directly to two other review authors (D Churchill, L Jones) from the trial statistician. J Thornton had no dealings with the acquisition, preparation or analysis of the GRIT trial data in this review.

Implications for research

Large trials are needed to confirm whether the benefits for the child associated with a policy of expectant care are real, and to provide reassurance that there is no increase in risk of morbidity or mortality for the mother.

AUTHORS' CONCLUSIONS

Implications for practice

These data are insufficient to reach any firm conclusions about the comparative effects of these alternative strategies for the care of women with severe early onset pre-eclampsia. Nevertheless, the apparent increase in some measures of neonatal morbidity associated with interventionist care suggests that early delivery would need to be justified by a realistic expectation of harm to the mother if the pregnancy was continued.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

GRIT 2003

Methods	Multi-centre randomised controlled trial. Setting: 69 hospitals in 13 European countries.
Participants	547 women (588 babies) recruited, outcomes were available on 547 mothers (587 babies) Inclusion criteria: pregnant women with fetal compromise between 24 and 36 weeks, an umbilical artery Doppler waveform recorded and clinical uncertainty whether immediate delivery was indicated
Interventions	Immediate delivery (n = 273) (IPD n = 141): deliver now, within 48 hrs to permit completion of a steroid course Delayed delivery (n = 274) (IPD n = 121): defer delivery, meaning until delivery could safely be delayed no longer
Outcomes	Infant survival to hospital discharge and the Griffith's development quotient at 2 years of age The trial was for compromised preterm fetus: a subset of women within this trial had severe PE. IPD were available for this subset and these are the data which have been extracted and analysed for this review. The outcomes for this subset were as follows For the woman: CS. For the baby: intraventricular haemorrhage and/or hypoxic ischaemic encephalopathy; Apgar score at 5 minutes; neonatal seizures; necrotising enterocolitis; ventilation; measures of long-term growth and development (e.g. CP diagnosis, Griffiths score); gestational age at birth.
Notes	Only a subset of IPD data were included and analysed in this review (women with hypertension plus either proteinuria or IUGR)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A paper based number sequence with balanced blocks of 8-12 weeks used except during office hours when a computer-generated sequence was used."
Allocation concealment (selection bias)	Low risk	"An independent programmer organised allocation, using both randomisation and minimisation." "The process was designed to mask allocation from participating clin-

GRIT 2003 (*Continued*)

		icians, including those with access to the central trial office."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind - but most of the outcomes not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Some blinding of outcome assessment for long-term outcomes such as Griffiths assessment: "Assessors were masked to the child's group allocations"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A subset of IPD data was provided of women with severe PE (n = 262 - hypertension and IUGR and/or proteinuria). It is not possible to tell how complete this data set is, as it was provided by the authors of the original study
Selective reporting (reporting bias)	Low risk	All expected outcomes appear to have been reported upon.
Other bias	Unclear risk	Unclear. Other bias may have been introduced as only a subset of the original randomised sample has provided data for analysis

Mesbah 2003

Methods	Randomisation was generated from a random number sequence table. Blind allocation was made using consecutively sealed envelopes. Odd numbers = aggressive management, even numbers = expectant management. Analysis was by ITT. Follow-up was judged to be 100%
Participants	30 pregnant women with severe PE between 28 and 33 + 6 days gestation. Severe PE was defined as a BP > 180/120 mmHg on 2 occasions 30 minutes apart; or a BP between 160 to 180/110 to 120 mmHg on 2 occasions 6 hrs apart. All participants had > 500 mg of proteinuria on a 24 hr urine collection measure. Exclusions were women who needed delivery for either a maternal or fetal condition in the 1st 24 hrs
Interventions	The group assigned to aggressive management were given steroids and then allowed 48 hrs to lapse before either an induction of labour was attempted or CS carried out. Women assigned to expectant management also had steroids but were then managed conservatively with bed rest, observations and nifedipine to control their BP. The indications for delivery in expectant management were, imminent eclampsia, deteriorating renal function, spontaneous preterm labour, absent EDF or a non-reassuring CTG, and reaching 34 weeks

Outcomes	Women: days of hospitalisation, imminent eclampsia, eclampsia, HELLP, CS, imminent eclampsia and deteriorating renal function Baby: days gained in utero, gestation at delivery, birthweight, admission to SCBU, SGA, stillbirth, neonatal death, 5-minute Apgar score
Notes	Although in table 2 the total number in the expectant arm is recorded as 10 participants, however, the detail of the table and percentages use the denominator 15. The total looks as if it is a typographical error. Information is being sought from the author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random sequence generated by going through random number tables till we obtained 30 pairs of numbers from 01 to 30. "
Allocation concealment (selection bias)	Low risk	"Randomly assigned to one of two management groups by withdrawing the next envelope in a series of 30 consecutively numbered, sealed, opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	41 women were recruited - but 11 (27%) judged too compromised for expectant management and were delivered by CS 5 patients from the expectant group appear to be missing from results table 2 - no explanation
Selective reporting (reporting bias)	Low risk	All expected outcomes appear to be reported.
Other bias	High risk	Severe group were excluded from the study and no baseline characteristics described for this group of patients. 5 patients missing from results for expectant group and no explanation given in the text

Odendaal 1990

Methods	Described as 'randomised'. No further information. Blinding in the assessment of outcome not mentioned. Analysis - ITT basis. Follow-up - 100%
Participants	38 women with severe PE at 28-34 weeks' gestation. Severe PE defined in 4 ways, depending on BP, proteinuria and symptoms. Women were either already admitted for bed rest and later met criteria, or admitted because of severe PE and after 48 hrs stabilisation met entry criteria. 10 primigravidae per group. Exclusions: oral antihypertensives before trial entry. Fetal or maternal complications within 48 hrs (20 women excluded before randomisation for this reason)
Interventions	All eligible women in 48 hrs before trial entry: MgSO4 for 24 hrs. If BP 160/110 mmHg, or more, 6.25 mg dihydralazine boluses. If steroids not already given, betamethasone 12 mg IM and again after 24 hrs Interventionist: delivery by either CS or by induction of labour, depending on obstetric circumstances. If cervix not favourable, prostaglandin E2 tablets. If still not favourable after 24 hrs, CS. Expectant: bed rest on high-risk obstetric ward, BP controlled with prazosin, weekly betamethasone. Maternal and fetal condition monitored intensively. Delivery as 34 weeks, unless indicated earlier
Outcomes	Women: CS, abruption. Baby: stillbirth, neonatal death, HMD, NEC, pneumothorax, ventilation, days in NICU (mean), birthweight (mean), gestation at delivery (mean)
Notes	8 women in the interventionist group and 5 in the expectant group deteriorated while in hospital on bed rest and were randomised immediately. The trial recruited from January 1986 to January 1988.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	58 women eligible with severe PE; 20 had to be delivered before randomisation because of severe maternal complications or fetal distress.

Odendaal 1990 (*Continued*)

		20 were randomised to the aggressive-management group; 18 were randomised to the expectant group - not clear from results tables how many analysed - but presume no loss to follow-up as not described in the text ITT not stated.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported upon.
Other bias	Low risk	Groups seem similar - including 20 women excluded prior to randomisation (correspondence with author)

Sibai 1994

Methods	Randomisation was by computer-generated random number. Concealment of allocation by consecutively-numbered sealed, opaque, envelopes. Analysis - ITT basis. Follow-up - 100%
Participants	95 women with severe PE at 28-32 weeks' gestation. Severe PE defined as a persistent elevation of BP >/= 160/110 mmHg, proteinuria > 500 mg in 24 hrs and uric acid > 5 mg/dL. Exclusions: associated medical conditions, renal failure, diabetes or connective tissue disorders, associated obstetric complications, multiple pregnancies and preterm labour
Interventions	All eligible women in 24 hrs before trial entry: betamethasone 12 mg, repeated after 24 hrs, MgSO4 for 24 hrs. If BP 160/110 mmHg or more, hydralazine or nifedipine depending on clinician preference Interventionist: delivery by either CS or by induction of labour, on the basis of their obstetric condition. Expectant: maternal and fetal monitoring on an antenatal ward. If either the maternal or fetal condition deteriorated or they reached 34 weeks' gestation, delivery using the most appropriate method
Outcomes	Women: eclampsia, gestation at delivery (mean), CS, placental abruption, HELLP syndrome, renal failure, pulmonary oedema, postpartum length of stay. Baby: birthweight (mean), admission to NICU, length of stay in NICU, SGA, RDS, NEC, bronchopulmonary dysplasia, cerebral haemorrhage
Notes	The trial recruited from January 1991 to July 1993.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated random assignments."

Sibai 1994 (*Continued*)

Allocation concealment (selection bias)	Low risk	"Consecutively numbered, sealed, opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	129 women had severe PE, but 32 of these were ineligible because they met 1 or more of the exclusion criteria and 2 refused to participate - 95 women were randomised (expectant management n = 49; aggressive management n = 46). All women appear to have been accounted for in the results. Appears to be ITT.
Selective reporting (reporting bias)	Low risk	All expected outcomes appear to have been reported upon.
Other bias	Low risk	The 2 groups were similar with respect to clinical and laboratory findings

BP: blood pressure
CP: cerebral palsy
CS: caesarean section
CTG: cardiotocography
EDF: end diastolic flow
HELLP: haemolysis elevated liver enzymes and lowered platelets
HMD: hyaline membrane disease
hrs: hours
IM: intramuscular
IPD: individual patient data
ITT: intention-to-treat
IUGR: intrauterine growth restriction
MgSO4: magnesium sulphate
NEC: necrotising enterocolitis
NICU: neonatal intensive care unit
PE: pre-eclampsia
RDS: respiratory distress syndrome
SCBU: special care baby unit
SGA: small-for-gestational age

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

Study	Reason for exclusion
Gruppo di Studio1998	Not women with severe pre-eclampsia. This randomised trial compared routine treatment with calcium channel blockers in mild to moderate hypertension
Langenveld 2011	Not women with severe pre-eclampsia. This multi-centre, randomised trial compared induction of labour versus expectant monitoring for gestation hypertension or mild pre-eclampsia

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

Duvekot 2011

Trial name or title	TOTEM study (temporise or terminate pregnancy in women with severe pre-eclampsia at 28-34 weeks): a study protocol
Methods	Randomised controlled trial. Multi-centre trial - women admitted in all Dutch tertiary care hospitals
Participants	Women with severe pre-eclampsia, gestational age at inclusion of 27.6 to 33.5 weeks, singleton pregnancy, estimated fetal weight 500 g and no known major fetal congenital abnormalities
Interventions	Delivery at least 48 hours after admission (described as "termination of pregnancy") OR expectant management
Outcomes	**Primary outcomes**: composite major maternal and neonatal morbidity and mortality Short-term maternal outcome is defined as the occurrence of major complications (pulmonary oedema, encephalopathy/eclampsia, acute respiratory distress syndrome, cerebrovascular incident, abruption placentae, liver haematoma/liver rupture, acute fatty liver of pregnancy, severe renal insufficiency, thromboembolism) **Secondary outcomes:** long-term neonatal outcome using Bailey-3 assessment and maternal long-term outcome defined as persistent morbidity
Starting date	Randomisation during 60 months. Start randomisation June 2011
Contact information	Duvekot JJ et al on behalf of the TOTEM study collaboration group Erasmus MC, Rotterdam, The Netherlands
Notes	

DATA AND ANALYSES

Comparison 1. Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eclampsia	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 HELLP syndrome	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.05, 5.68]
3 Pulmonary oedema	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Death of the baby (all stillbirths, neonatal and infant deaths)	4	425	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.69, 1.71]
5 Death of the baby (subgrouped by time of death)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Stillbirth	4	425	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.03, 1.16]
5.2 Perinatal death	2	68	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.45, 2.89]
5.3 Neonatal death	4	425	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.80, 2.23]
5.4 Death after 28 days	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.8 [0.18, 18.21]
6 Intraventricular haemorrhage or hypoxic ischaemic encephalopathy	1	262	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.06, 3.14]
7 Renal failure	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 6.97]
8 Caesarean section	4	425	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.01, 1.18]
9 Placental abruption	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.26, 2.40]
10 Low Apgar score at five minutes (< 7 at five minutes)	1	262	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.87, 2.50]
11 Neonatal seizures	1	262	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.27, 24.43]
12 Hyaline membrane disease	2	133	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [1.39, 3.81]
13 Necrotising enterocolitis	3	395	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [0.93, 4.79]
14 Baby ventilated	2	300	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.11, 2.02]
15 Measures of long-term growth & development (cerebral palsy)	1	262	Risk Ratio (M-H, Fixed, 95% CI)	6.01 [0.75, 48.14]
16 Measures of long-term growth & development (poor hearing/hearing aid)	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.07, 1.74]
17 Measures of long-term growth & development (impaired vision)	1	262	Risk Ratio (M-H, Fixed, 95% CI)	4.29 [0.51, 36.22]
18 Small-for-gestational age	2	125	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.14, 0.65]
19 Gestation at birth (days)	4	425	Mean Difference (IV, Random, 95% CI)	-9.91 [-16.37, -3.45]
20 Length of stay in neonatal intensive care unit (days)	2	125	Mean Difference (IV, Random, 95% CI)	11.14 [1.57, 20.72]
21 Admission to neonatal intensive care unit	2	125	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.16, 1.58]

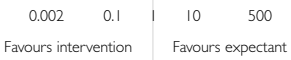
Analysis 1.1. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 1 Eclampsia.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 1 Eclampsia

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Sibai 1994	0/46	0/49		0.0 [0.0, 0.0]
Total (95% CI)	**46**	**49**		**0.0 [0.0, 0.0]**
Total events: 0 (Interventionist), 0 (Expectant)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				



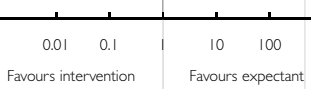
Analysis 1.2. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 2 HELLP syndrome.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 2 HELLP syndrome

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sibai 1994	1/46	2/49		100.0 %	0.53 [0.05, 5.68]
Total (95% CI)	**46**	**49**		**100.0 %**	**0.53 [0.05, 5.68]**
Total events: 1 (Interventionist), 2 (Expectant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					
Test for subgroup differences: Not applicable					



Analysis 1.3. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 3 Pulmonary oedema.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 3 Pulmonary oedema

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Sibai 1994	0/46	0/49		0.0 [0.0, 0.0]
Total (95% CI)	**46**	**49**		**0.0 [0.0, 0.0]**

Total events: 0 (Interventionist), 0 (Expectant)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 4 Death of the baby (all stillbirths, neonatal and infant deaths).

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 4 Death of the baby (all stillbirths, neonatal and infant deaths)

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Sibai 1994	0/46	0/49		0.0 [0.0, 0.0]
Odendaal 1990	5/20	3/18		1.50 [0.42, 5.41]
Mesbah 2003	6/15	4/15		1.50 [0.53, 4.26]
GRIT 2003	22/141	20/121		0.94 [0.54, 1.64]
Total (95% CI)	**222**	**203**		**1.08 [0.69, 1.71]**

Total events: 33 (Interventionist), 27 (Expectant)
Heterogeneity: Chi^2 = 0.86, df = 2 (P = 0.65); I^2 =0.0%
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 5 Death of the baby (subgrouped by time of death).

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 5 Death of the baby (subgrouped by time of death)

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Stillbirth				
Sibai 1994	0/46	0/49		0.0 [0.0, 0.0]
Mesbah 2003	0/15	0/15		0.0 [0.0, 0.0]
Odendaal 1990	0/20	1/18		0.30 [0.01, 6.97]
GRIT 2003	1/141	5/121		0.17 [0.02, 1.45]
Subtotal (95% CI)	**222**	**203**		**0.20 [0.03, 1.16]**
Total events: 1 (Interventionist), 6 (Expectant)				
Heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.77); I^2 =0.0%				
Test for overall effect: Z = 1.79 (P = 0.073)				
2 Perinatal death				
Odendaal 1990	1/20	2/18		0.45 [0.04, 4.55]
Mesbah 2003	6/15	4/15		1.50 [0.53, 4.26]
Subtotal (95% CI)	**35**	**33**		**1.14 [0.45, 2.89]**
Total events: 7 (Interventionist), 6 (Expectant)				
Heterogeneity: Chi^2 = 0.89, df = 1 (P = 0.35); I^2 =0.0%				
Test for overall effect: Z = 0.27 (P = 0.79)				
3 Neonatal death				
Sibai 1994	0/46	0/49		0.0 [0.0, 0.0]
Odendaal 1990	3/20	1/18		2.70 [0.31, 23.69]
Mesbah 2003	6/15	4/15		1.50 [0.53, 4.26]
GRIT 2003	21/141	15/121		1.20 [0.65, 2.23]
Subtotal (95% CI)	**222**	**203**		**1.33 [0.80, 2.23]**
Total events: 30 (Interventionist), 20 (Expectant)				
Heterogeneity: Chi^2 = 0.56, df = 2 (P = 0.75); I^2 =0.0%				

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Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.09 (P = 0.28)				
4 Death after 28 days				
Odendaal 1990	2/20	1/18		1.80 [0.18, 18.21]
Subtotal (95% CI)	**20**	**18**		**1.80 [0.18, 18.21]**
Total events: 2 (Interventionist), 1 (Expectant)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.50 (P = 0.62)				

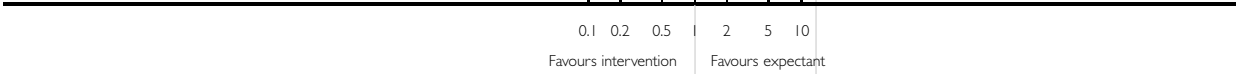
Analysis 1.6. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 6 Intraventricular haemorrhage or hypoxic ischaemic encephalopathy.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 6 Intraventricular haemorrhage or hypoxic ischaemic encephalopathy

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GRIT 2003	34/141	16/121		100.0 %	1.82 [1.06, 3.14]
Total (95% CI)	**141**	**121**		**100.0 %**	**1.82 [1.06, 3.14]**
Total events: 34 (Interventionist), 16 (Expectant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.17 (P = 0.030)					
Test for subgroup differences: Not applicable					



Analysis 1.7. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 7 Renal failure.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 7 Renal failure

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Odendaal 1990	0/20	1/18		0.30 [0.01, 6.97]
Sibai 1994	0/46	0/49		0.0 [0.0, 0.0]
Total (95% CI)	**66**	**67**		**0.30 [0.01, 6.97]**

Total events: 0 (Interventionist), 1 (Expectant)
Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 8 Caesarean section.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 8 Caesarean section

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mesbah 2003	11/15	9/15		5.1 %	1.22 [0.73, 2.04]
Odendaal 1990	14/20	15/18		9.0 %	0.84 [0.59, 1.20]
Sibai 1994	39/46	36/49		19.9 %	1.15 [0.94, 1.42]
GRIT 2003	137/141	107/121		65.9 %	1.10 [1.02, 1.18]
Total (95% CI)	**222**	**203**		**100.0 %**	**1.09 [1.01, 1.18]**

Total events: 201 (Interventionist), 167 (Expectant)
Heterogeneity: $Chi^2 = 2.60$, df = 3 (P = 0.46); $I^2 = 0.0\%$
Test for overall effect: Z = 2.33 (P = 0.020)
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 9 Placental abruption.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 9 Placental abruption

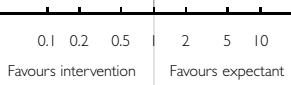
Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sibai 1994	2/46	2/49		31.5 %	1.07 [0.16, 7.25]
Odendaal 1990	3/20	4/18		68.5 %	0.68 [0.17, 2.62]
Total (95% CI)	**66**	**67**		**100.0 %**	**0.80 [0.26, 2.40]**

Total events: 5 (Interventionist), 6 (Expectant)

Heterogeneity: $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 10 Low Apgar score at five minutes (< 7 at five minutes).

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 10 Low Apgar score at five minutes (< 7 at five minutes)

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GRIT 2003	31/141	18/121		100.0 %	1.48 [0.87, 2.50]
Total (95% CI)	**141**	**121**		**100.0 %**	**1.48 [0.87, 2.50]**
Total events: 31 (Interventionist), 18 (Expectant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
Test for subgroup differences: Not applicable					

Analysis 1.11. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 11 Neonatal seizures.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 11 Neonatal seizures

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GRIT 2003	3/141	1/121		100.0 %	2.57 [0.27, 24.43]
Total (95% CI)	**141**	**121**		**100.0 %**	**2.57 [0.27, 24.43]**
Total events: 3 (Interventionist), 1 (Expectant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.82 (P = 0.41)					
Test for subgroup differences: Not applicable					

Analysis 1.12. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 12 Hyaline membrane disease.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 12 Hyaline membrane disease

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Odendaal 1990	11/20	4/18		28.3 %	2.48 [0.96, 6.41]
Sibai 1994	23/46	11/49		71.7 %	2.23 [1.23, 4.04]
Total (95% CI)	**66**	**67**		**100.0 %**	**2.30 [1.39, 3.81]**

Total events: 34 (Interventionist), 15 (Expectant)

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 3.23 (P = 0.0012)

Test for subgroup differences: Not applicable

Analysis 1.13. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 13 Necrotising enterocolitis.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 13 Necrotising enterocolitis

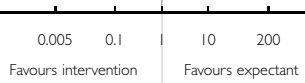
Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sibai 1994	5/46	0/49		6.1 %	11.70 [0.67, 205.88]
Odendaal 1990	3/20	1/18		13.2 %	2.70 [0.31, 23.69]
GRIT 2003	9/141	6/121		80.8 %	1.29 [0.47, 3.51]
Total (95% CI)	**207**	**188**		**100.0 %**	**2.10 [0.93, 4.79]**

Total events: 17 (Interventionist), 7 (Expectant)

Heterogeneity: Chi^2 = 2.35, df = 2 (P = 0.31); I^2 =15%

Test for overall effect: Z = 1.77 (P = 0.076)

Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 14 Baby ventilated.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 14 Baby ventilated

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Odendaal 1990	7/20	2/18		4.7 %	3.15 [0.75, 13.25]
GRIT 2003	66/141	40/121		95.3 %	1.42 [1.04, 1.93]
Total (95% CI)	**161**	**139**		**100.0 %**	**1.50 [1.11, 2.02]**

Total events: 73 (Interventionist), 42 (Expectant)

Heterogeneity: Chi^2 = 1.15, df = 1 (P = 0.28); I^2 =13%

Test for overall effect: Z = 2.62 (P = 0.0089)

Test for subgroup differences: Not applicable

Analysis 1.15. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 15 Measures of long-term growth & development (cerebral palsy).

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 15 Measures of long-term growth % development (cerebral palsy)

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GRIT 2003	7/141	1/121		100.0 %	6.01 [0.75, 48.14]
Total (95% CI)	**141**	**121**		**100.0 %**	**6.01 [0.75, 48.14]**

Total events: 7 (Interventionist), 1 (Expectant)

Heterogeneity: not applicable

Test for overall effect: Z = 1.69 (P = 0.091)

Test for subgroup differences: Not applicable

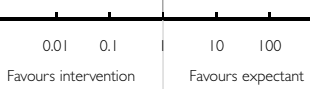
Analysis 1.16. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 16 Measures of long-term growth & development (poor hearing/hearing aid).

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 16 Measures of long-term growth % development (poor hearing/hearing aid)

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GRIT 2003	2/141	5/121		100.0 %	0.34 [0.07, 1.74]
Total (95% CI)	**141**	**121**		**100.0 %**	**0.34 [0.07, 1.74]**
Total events: 2 (Interventionist), 5 (Expectant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					
Test for subgroup differences: Not applicable					



Analysis 1.17. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 17 Measures of long-term growth & development (impaired vision).

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 17 Measures of long-term growth % development (impaired vision)

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
GRIT 2003	5/141	1/121		100.0 %	4.29 [0.51, 36.22]
Total (95% CI)	**141**	**121**		**100.0 %**	**4.29 [0.51, 36.22]**

Total events: 5 (Interventionist), 1 (Expectant)
Heterogeneity: not applicable
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable

Analysis 1.18. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 18 Small-for-gestational age.

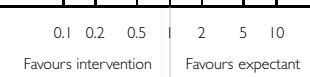
Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 18 Small-for-gestational age

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mesbah 2003	2/15	9/15		38.3 %	0.22 [0.06, 0.86]
Sibai 1994	5/46	15/49		61.7 %	0.36 [0.14, 0.90]
Total (95% CI)	**61**	**64**		**100.0 %**	**0.30 [0.14, 0.65]**

Total events: 7 (Interventionist), 24 (Expectant)
Heterogeneity: Chi^2 = 0.31, df = 1 (P = 0.58); I^2 =0.0%
Test for overall effect: Z = 3.06 (P = 0.0022)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 19 Gestation at birth (days).

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

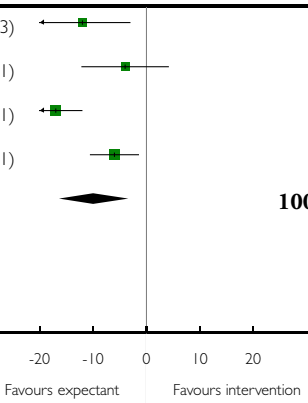
Outcome: 19 Gestation at birth (days)

Study or subgroup	Interventionist N	Mean(SD)	Expectant N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Odendaal 1990	20	211 (15)	18	223 (13)		20.7 %	-12.00 [-20.90, -3.10]
Mesbah 2003	15	213 (12)	15	217 (11)		22.0 %	-4.00 [-12.24, 4.24]
Sibai 1994	46	216 (14)	49	233 (11)		28.2 %	-17.00 [-22.08, -11.92]
GRIT 2003	141	217 (17)	121	223 (21)		29.0 %	-6.00 [-10.68, -1.32]
Total (95% CI)	**222**		**203**			**100.0 %**	**-9.91 [-16.37, -3.45]**

Heterogeneity: $Tau^2 = 31.74$; $Chi^2 = 12.30$, df = 3 (P = 0.01); $I^2 = 76\%$

Test for overall effect: Z = 3.01 (P = 0.0026)

Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 20 Length of stay in neonatal intensive care unit (days).

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 20 Length of stay in neonatal intensive care unit (days)

Study or subgroup	Interventionist N	Mean(SD)	Expectant N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Sibai 1994	46	36.6 (17.4)	49	20.2 (14)		46.4 %	16.40 [10.02, 22.78]
Mesbah 2003	15	22.3 (5.8)	15	15.7 (4.5)		53.6 %	6.60 [2.89, 10.31]
Total (95% CI)	**61**		**64**			**100.0 %**	**11.14 [1.57, 20.72]**

Heterogeneity: $Tau^2 = 40.93$; $Chi^2 = 6.78$, df = 1 (P = 0.01); $I^2 = 85\%$

Test for overall effect: Z = 2.28 (P = 0.023)

Test for subgroup differences: Not applicable

Analysis 1.21. Comparison 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 21 Admission to neonatal intensive care unit.

Review: Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

Comparison: 1 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 21 Admission to neonatal intensive care unit

Study or subgroup	Interventionist n/N	Expectant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mesbah 2003	15/15	10/15		22.4 %	1.48 [1.02, 2.13]
Sibai 1994	46/46	37/49		77.6 %	1.32 [1.12, 1.55]
Total (95% CI)	**61**	**64**		**100.0 %**	**1.35 [1.16, 1.58]**

Total events: 61 (Interventionist), 47 (Expectant)

Heterogeneity: $Chi^2 = 0.31$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 3.93 (P = 0.000084)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. Search strategy

CENTRAL (*The Cochrane LIbrary* 2006, Issue 2)
#1 MeSH descriptor Pregnancy explode all trees in MeSH products
#2 MeSH descriptor Pregnancy Complications explode all trees in MeSH products
#3 preeclamp* in All Fields in all products
#4 pre-eclamp* in All Fields in all products
#5 pre next eclamp* in All Fields in all products
#6 eclamp* in All Fields in all products
#7 hypertens* in All Fields in all products
#8 #1 or #2
#9 #3 or #4 or #5 or #6 or #7
#10 aggressive near management in All Fields in all products
#11 early near delivery in All Fields in all products
#12 expectant near management in All Fields in all products
#13 delayed near delivery in All Fields in all products
#14 #10 or #11 or #12 or #13
#15 #8 and #9 and #14

Appendix 2. Methods used to assess trials included in previous versions of this review

The following methods were used to assess Odendaal 1990 and Sibai 1994.
Two review authors assessed potentially eligible trials for their suitability for inclusion in the review. Decisions regarding inclusion were made separately and results compared. Any disagreement was resolved through discussion. Data were extracted by two authors using an agreed format, and again discrepancies resolved through discussion. If agreement could not be reached that item was excluded until further information was available from the trialists. Data were entered by one author, and double checked by the other.
Validity of each included trial was assessed according to the criteria outlined in the Cochrane Reviewers' Handbook (Higgins 2005). Trials were assessed with a grade allocated to each trial on the basis of allocation concealment: A (adequate), B (unclear), or C (clearly inadequate). Where the method of allocation concealment was unclear, attempts were made to contact authors to provide further details. Quasi-randomised designs, such as alternate allocation and use of record numbers, were excluded.
Blinding and completeness of follow-up were assessed for each outcome using the following criteria:
For completeness of follow-up:
A. less than 3% of participants excluded;
B. 3% to 9.9% of participants excluded;
C. 10% to 19.9% of participants excluded.
Excluded: if not possible to present the data by intention to treat or if more than 20% of participants were excluded.
For blinding of assessment of outcome:
A. double blind;
B. single blind;
C. no blinding or blinding not mentioned.
Excluded: no blinding and the outcome very subjective.

Statistical analyses were carried out using the Review Manager software (RevMan 2000) with results presented as summary relative risk, risk difference and number needed to treat. Tests of heterogeneity between trials were applied to assess the significance of any differences between trials and possible causes of any heterogeneity were explored.
Wherever possible, subgroup analyses for the main outcomes were performed by gestation at trial entry (24 to 28 weeks and 29 to 34 weeks), severity of pre-eclampsia (HELLP syndrome or imminent eclampsia and neither of these).

WHAT'S NEW

Last assessed as up-to-date: 10 July 2013.

Date	Event	Description
10 July 2013	New citation required and conclusions have changed	Expectant management may be associated with decreased morbidity for the baby
28 February 2013	New search has been performed	Search updated. Methods updated. Three studies identified from updated search (Duvekot 2011; GRIT 2003; Langenveld 2011). One study has been included (GRIT 2003); one is an ongoing study (Duvekot 2011); and one study has been excluded (Langenveld 2011). One study previously in studies awaiting assessment in the last update has now been included (Mesbah 2003).

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 3, 2002

Date	Event	Description
16 February 2010	New search has been performed	Review updated with new report added to Characteristics of studies awaiting classification
1 December 2009	Amended	Search updated. One new report added to Studies awaiting classification (Mesbah 2003a)
15 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Lelia Duley and David Churchill contributed to the development of the protocol. Both authors assessed potentially eligible studies for inclusion in the first version of this review, and extracted data. D Churchill entered data, and these were checked by L Duley. Both authors contributed to writing the review.

For the 2013 update, Leanne Jones updated the methods and assessed studies for inclusion, extracted data, entered data, and these were checked by David Churchill. Leanne Jones wrote the first draft of the updated results. David Churchill, Lelia Duley and Jim Thornton commented on all drafts of the 2013 update and made edits.

DECLARATIONS OF INTEREST

Jim Thornton is an author on one of the included studies (GRIT 2003). However, he was not involved in any assessment, data extraction or data analysis of this trial.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

UK NIHR Programme of centrally-managed pregnancy and childbirth systematic reviews of priority to the NHS and users of the NHS: 10/4001/02

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In 2013, the methods were updated. The inclusion criteria were modified to define more clearly the criteria for types of participants:

Women with severe pre-eclampsia before or equal to 34 weeks' gestation. Severe pre-eclampsia was defined as high blood pressure, $\geq$ 140/90 mmHg on two consecutive occasions four or more hours apart and proteinuria greater than 300 mg/24 hours. Alternatively as:

- severe hypertension (blood pressure at least 160 mmHg systolic, or 110 mmHg diastolic) alone;

or hypertension as defined above plus one or more of the following criteria:

- severe proteinuria (usually at least 3 g (range 2 g to 5 g) protein in 24 hours, or 3+ on dipstick);
- reduced urinary volume (less than 500 mL in 24 hours), upper abdominal pain, pulmonary oedema;
- neurological disturbances (such as headache, visual disturbances, and exaggerated tendon reflexes);
- impaired liver function tests, high serum creatinine, low platelets;
- suspected intrauterine growth restriction or reduced liquor volume.

This latter set of criteria reflect the natural history of the disease and clinical practice when diagnosing severe pre-eclampsia.

Primary and secondary outcomes were defined.

INDEX TERMS

Medical Subject Headings (MeSH)

*Delivery, Obstetric; Enterocolitis, Necrotizing [etiology]; Hyaline Membrane Disease [etiology]; Infant, Newborn; Pre-Eclampsia [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy