Interventionist versus expectant care for severe pre-eclampsia before term (Review)

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ABSTRACT

Background
Severe pre-eclampsia can cause significant mortality and morbidity for both mother and child, particularly when it occurs well before term. The only known cure for this disease is delivery. Some obstetricians advocate early delivery to prevent the development of serious maternal complications, such as eclampsia (fits) and kidney failure. Others prefer a more expectant approach in an attempt to delay delivery and, hopefully, 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 strategy
We searched the Cochrane Pregnancy and Childbirth Group Trials Register (April 2006) and the Cochrane Controlled Trials Register (*The Cochrane Library* 2006, Issue 2).

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

Data collection and analysis
Both review authors independently extracted and checked data.

Main results
Two trials (133 women) are included in this review. There are insufficient data for reliable conclusions about the comparative effects on outcome for the mother. For the baby, there is insufficient evidence for reliable conclusions about the effects on stillbirth or death after delivery (relative risk (RR) 1.50, 95% confidence interval (CI) 0.42 to 5.41). Babies whose mothers had been allocated to the interventionist group had more hyaline membrane disease (RR 2.30, 95% CI 1.39 to 3.81), more necrotising enterocolitis (RR 5.54, 95% CI 1.04 to 29.56) and were more likely to need admission to neonatal intensive care (RR 1.32, 95% CI 1.13 to 1.55) than those allocated an expectant policy. Nevertheless, babies allocated to the interventionist policy were less likely to be small-for-gestational age (RR 0.36, 95% CI 0.14 to 0.90). There were no statistically significant differences between the two strategies for any other outcomes.

Authors' conclusions
There are insufficient data for any reliable recommendation about which policy of care should be used for women with severe early onset pre-eclampsia. Further large trials are needed.

PLAIN LANGUAGE SUMMARY

Little evidence exists to show whether early delivery is better than expectant care for women who suffer from severe pre-eclampsia before 34 weeks of pregnancy

Women who develop early onset pre-eclampsia (high blood pressure and protein in the urine) and their unborn babies, are at risk of severe complications and even death. The only known cure for pre-eclampsia is delivery of the baby and placenta. However, being born too early can in itself have problems for the baby, even with the administration of corticosteroids to help mature the baby's lungs. This review found that there is not enough evidence from the trials performed to recommend either early delivery or expectant care for women with severe pre-eclampsia before 34 weeks of pregnancy.

BACKGROUND

Pre-eclampsia is a multisystem disorder, usually associated with raised blood pressure and proteinuria (usually defined as greater than 300 mg in a 24 hour urine collection, or as 1+ or more on dipstick testing) (Davey 1988). In its mild form, it affects three per cent of pregnant women and for many women with mild pre-eclampsia the outcome is good with a healthy baby and mother. The severe form of pre-eclampsia affects about one to two per cent of pregnant women (Brown 1997). When severe, it can involve the woman's liver, kidneys, clotting system, or brain as well as the placenta (Australasian 1993; Gifford 1990) and can lead to death or serious problems for the woman, her child, or both. Pre-eclampsia is one of the more common complications of pregnancy, and can occur at any time during the second half of pregnancy or the first few days after delivery. If severe pre-eclampsia occurs after delivery, the woman should receive appropriate supportive care until the condition resolves, which is usually within a few days. Usually, severe pre-eclampsia occurs before delivery and the only known definitive treatment is to end the pregnancy by delivering the baby and placenta. When the baby is still immature, the decision about when is best to deliver can be difficult. It involves a difficult balance between the risks to the woman of continuing the pregnancy and the risks to the baby of being born too soon.

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. 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.

This serious 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 2002), prophylactic anticonvulsants (Duley 2003) and plasma volume expansion (Duley 1999b). Prevention of pre-eclampsia is covered by reviews of calcium supplementation (Hofmeyr 2002), antiplatelets (Knight 2000), 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 sufficient 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.

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 term. Whenever possible, women were stratified into two groups based upon gestation at trial entry. These groups are 24 to 28 weeks' and 29 to 34 weeks' gestation.

Types of intervention

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

For the woman: death, eclampsia (fitting), stroke (brain damage), renal failure (kidney failure), liver failure, HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome, pulmonary oedema (fluid in the lungs), cardiac arrest, the need for invasive monitoring, such as central venous catheterisation (intravenous lines into the great veins around the heart), caesarean section.

For the baby: stillbirth, neonatal death, low Apgar score at five minutes, neonatal seizures, intraventricular haemorrhage (bleeding in the brain), hyaline membrane disease (stiff lungs), pneumothorax (air leaks from the lungs), necrotising enterocolitis (bleeding into the bowel wall) and ventilation for more than seven days. Also, measures of long-term growth and development, such as important impairment and cerebral palsy.

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, ventilation for the baby, surfactant for the baby.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (April 2006).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched The Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 2) using the following strategy:

#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

We did not apply any language restrictions.

METHODS OF THE REVIEW

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).

DESCRIPTION OF STUDIES

Two trials with a total of 133 women are included in this review. In both trials, women had a 24 to 48 hour period of stabilisation during which they were given steroids to accelerate fetal lung maturity, magnesium sulphate and antihypertensives if necessary to lower blood pressure. If they continued to meet the eligibility criteria at the end of this period they were then randomised. In both studies, women in the expectant group were delivered when they reached 34 weeks' gestation. Earlier delivery in this expectant group was implemented if either the maternal or fetal condition deteriorated, as determined by prespecified criteria. Neither study assessed the long term outcomes for either the baby or the mother.

For further details *see* 'Characteristics of included studies'.

METHODOLOGICAL QUALITY

Only two trials met the criteria for the review. Both were relatively small. For one study, the method used to conceal the allocation was not described (South Africa 1990); in the other, concealment was adequate (USA 1994). Only women with truly severe pre-eclampsia were entered into both trials. In the larger study (USA 1994) women with co-existent medical problems were excluded. This was not discussed in the other trial. Several outcomes are reported only by one trial.

RESULTS

Two trials with a total of 133 women are included in this review. There are insufficient data for any reliable conclusions about the effects of these alternative polices on outcome for the mother.

For the baby, there is insufficient evidence for any reliable conclusions about the effects on stillbirth or death after delivery (two trials, 133 women, relative risk (RR) 1.50, 95% confidence interval (CI) 0.42 to 5.41). 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), more necrotising enterocolitis (two trials, 133 women, RR 5.54, 95% CI 1.04 to 29.56) and were more likely to need admission to neonatal intensive care (one trial, 95 women, RR 1.32, 95% CI 1.13 to 1.55) than those allocated an expectant policy. Nevertheless, babies allocated to the interventionist policy were less likely to be small-for-gestational age (one trial, 95 women, RR 0.36, 95% CI 0.14 to 0.90). There were no statistically significant differences between the two management strategies for any other outcomes.

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 if the pregnancy is continued have to be constantly balanced against the hazards of prematurity to the fetus if it is delivered too early. Most obstetricians would probably be cautious and expedite delivery in favour of the outcome for the mother. What is not clear is to what level this adversely (if at all) affects the baby.

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, as it contains only two small trials and the confidence intervals for all outcomes are wide. However, the evidence is promising that short-term morbidity for the baby may be reduced by a policy of expectant care. Before this policy can be recommended for clinical practice, further evidence is required to demonstrate that any short-term benefit continues in the longer term, and to provide reassurance that there is no increase in mortality for the child, or in morbidity 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.

Implications for research

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

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

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SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Medical Research Council UK

REFERENCES

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TABLES

Characteristics of included studies

Study	South Africa 1990
Methods	Described as 'randomised'. No further information. Blinding in the assessment of outcome not mentioned. Analysis - intention to treat basis. Follow up - 100%.

Characteristics of included studies (*Continued*)

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.
Allocation concealment	B – Unclear

Study	**USA 1994**
Methods	Randomisation was by computer-generated random number. Concealment of allocation by consecutively-numbered sealed, opaque, envelopes. Analysis - intention to treat 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.
Allocation concealment	A – Adequate

BP: blood pressure
CS: caesearean section
HELLP: haemolysis elevated liver enzymes and lowered platelets
HMD: hyaline membrane disease
hrs: hours
IM: intramuscular
MgSO4: magnesium sulphate
NEC: necrotising enterocolitis
NICU: neonatal intensive care unit
PE: pre-eclampsia
RDS: respiratory distress syndrome
SGA: small-for-gestational age

Characteristics of excluded studies

Study	Reason for exclusion
Italy 1998	Not women with severe pre-eclampsia.
	This randomised trial compared routine treatment with calcium channel blockers in mild to moderate hypertension.

ANALYSES

Comparison 01. Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Eclampsia	1	95	Relative Risk (Fixed) 95% CI	Not estimable
02 Renal failure	2	133	Relative Risk (Fixed) 95% CI	0.30 [0.01, 6.97]
04 Pulmonary oedema	1	95	Relative Risk (Fixed) 95% CI	Not estimable
05 HELLP syndrome	1	95	Relative Risk (Fixed) 95% CI	0.53 [0.05, 5.68]
06 Caesarean section	2	133	Relative Risk (Fixed) 95% CI	1.06 [0.88, 1.26]
07 Placental abruption	2	133	Relative Risk (Fixed) 95% CI	0.80 [0.26, 2.40]
08 Death of the baby (all stillbirths, neonatal and infant deaths)	2	133	Relative Risk (Fixed) 95% CI	1.50 [0.42, 5.41]
09 Death of the baby (subgrouped by time of death)			Relative Risk (Fixed) 95% CI	Subtotals only
10 Small-for-gestational age	1	95	Relative Risk (Fixed) 95% CI	0.36 [0.14, 0.90]
11 Hyaline membrane disease	2	133	Relative Risk (Fixed) 95% CI	2.30 [1.39, 3.81]
12 Necrotising enterocolitis	2	133	Relative Risk (Fixed) 95% CI	5.54 [1.04, 29.56]
13 Admission to neonatal intensive care unit	1	95	Relative Risk (Fixed) 95% CI	1.32 [1.13, 1.55]
14 Baby ventilated	1	38	Relative Risk (Fixed) 95% CI	3.15 [0.75, 13.25]
15 Length of stay in neonatal intensive care unit (days)	1	95	Weighted Mean Difference (Fixed) 95% CI	16.40 [10.02, 22.78]
16 Gestation at birth (days)	2	133	Weighted Mean Difference (Fixed) 95% CI	-15.77 [-20.19, -11.36]

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title Interventionist versus expectant care for severe pre-eclampsia before term

Authors Churchill D, Duley L

Contribution of author(s) Both review authors contributed to the development of the protocol. Both authors assessed potentially eligible studies for inclusion in the review, and extracted data. D Churchill

	entered data, and these were checked by L Duley. Both authors contributed to writing the review.
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What's New	April 2006 Search updated. No new trial reports identified.
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Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 01 Eclampsia

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 01 Eclampsia

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× USA 1994	0/46	0/49		0.0	Not estimable
Total (95% CI)	46	49		0.0	Not estimable
Total events: 0 (Interventionist), 0 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.02. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 02 Renal failure

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 02 Renal failure

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1990	0/20	1/18		100.0	0.30 [0.01, 6.97]
× USA 1994	0/46	0/49		0.0	Not estimable
Total (95% CI)	66	67		100.0	0.30 [0.01, 6.97]
Total events: 0 (Interventionist), 1 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.75 p=0.5					

Analysis 01.04. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 04 Pulmonary oedema

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 04 Pulmonary oedema

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× USA 1994	0/46	0/49		0.0	Not estimable
Total (95% CI)	46	49		0.0	Not estimable
Total events: 0 (Interventionist), 0 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.05. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 05 HELLP syndrome

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 05 HELLP syndrome

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 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)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.52 p=0.6					

Analysis 01.06. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 06 Caesarean section

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 06 Caesarean section

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1990	14/20	15/18		31.2	0.84 [0.59, 1.20]
USA 1994	39/46	36/49		68.8	1.15 [0.94, 1.42]
Total (95% CI)	66	67		100.0	1.06 [0.88, 1.26]

Total events: 53 (Interventionist), 51 (Expectant)

Test for heterogeneity chi-square=2.31 df=1 p=0.13 I^2 =56.7%

Test for overall effect z=0.60 p=0.6

Analysis 01.07. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 07 Placental abruption

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 07 Placental abruption

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1990	3/20	4/18		68.5	0.68 [0.17, 2.62]
USA 1994	2/46	2/49		31.5	1.07 [0.16, 7.25]
Total (95% CI)	66	67		100.0	0.80 [0.26, 2.40]

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

Test for heterogeneity chi-square=0.15 df=1 p=0.70 I^2 =0.0%

Test for overall effect z=0.40 p=0.7

Analysis 01.08. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 08 Death of the baby (all stillbirths, neonatal and infant deaths)

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 08 Death of the baby (all stillbirths, neonatal and infant deaths)

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1990	5/20	3/18		100.0	1.50 [0.42, 5.41]
× USA 1994	0/46	0/49		0.0	Not estimable
Total (95% CI)	66	67		100.0	1.50 [0.42, 5.41]
Total events: 5 (Interventionist), 3 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.62 p=0.5					

Analysis 01.09. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 09 Death of the baby (subgrouped by time of death)

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 09 Death of the baby (subgrouped by time of death)

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Stillbirth					
South Africa 1990	0/20	1/18		100.0	0.30 [0.01, 6.97]
× USA 1994	0/46	0/49		0.0	Not estimable
Subtotal (95% CI)	66	67		100.0	0.30 [0.01, 6.97]
Total events: 0 (Interventionist), 1 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.75 p=0.5					
02 Perinatal death					
South Africa 1990	1/20	2/18		100.0	0.45 [0.04, 4.55]
Subtotal (95% CI)	20	18		100.0	0.45 [0.04, 4.55]
Total events: 1 (Interventionist), 2 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					
03 Neonatal death					
South Africa 1990	3/20	1/18		100.0	2.70 [0.31, 23.69]

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Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× USA 1994	0/46	0/49		0.0	Not estimable
Subtotal (95% CI)	66	67		100.0	2.70 [0.31, 23.69]
Total events: 3 (Interventionist), 1 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.90 p=0.4					
04 Death after 28 days					
South Africa 1990	2/20	1/18		100.0	1.80 [0.18, 18.21]
Subtotal (95% CI)	20	18		100.0	1.80 [0.18, 18.21]
Total events: 2 (Interventionist), 1 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.50 p=0.6					

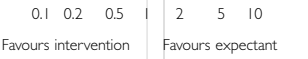
Analysis 01.10. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 10 Small-for-gestational age

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 10 Small-for-gestational age

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1994	5/46	15/49		100.0	0.36 [0.14, 0.90]
Total (95% CI)	46	49		100.0	0.36 [0.14, 0.90]
Total events: 5 (Interventionist), 15 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.19 p=0.03					



Analysis 01.11. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 11 Hyaline membrane disease

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 11 Hyaline membrane disease

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1990	11/20	4/18		28.3	2.48 [0.96, 6.41]
USA 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)

Test for heterogeneity chi-square=0.03 df=1 p=0.85 I^2 =0.0%

Test for overall effect z=3.23 p=0.001

Analysis 01.12. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 12 Necrotising enterocolitis

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

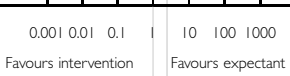
Outcome: 12 Necrotising enterocolitis

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1990	3/20	1/18		68.5	2.70 [0.31, 23.69]
USA 1994	5/46	0/49		31.5	11.70 [0.67, 205.88]
Total (95% CI)	66	67		100.0	5.54 [1.04, 29.56]

Total events: 8 (Interventionist), 1 (Expectant)

Test for heterogeneity chi-square=0.68 df=1 p=0.41 I^2 =0.0%

Test for overall effect z=2.00 p=0.05



Analysis 01.13. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 13 Admission to neonatal intensive care unit

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 13 Admission to neonatal intensive care unit

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1994	46/46	37/49		100.0	1.32 [1.13, 1.55]
Total (95% CI)	46	49		100.0	1.32 [1.13, 1.55]
Total events: 46 (Interventionist), 37 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.45 p=0.0006					

Analysis 01.14. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 14 Baby ventilated

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 14 Baby ventilated

Study	Interventionist n/N	Expectant n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1990	7/20	2/18		100.0	3.15 [0.75, 13.25]
Total (95% CI)	20	18		100.0	3.15 [0.75, 13.25]
Total events: 7 (Interventionist), 2 (Expectant)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.57 p=0.1					

Analysis 01.15. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 15 Length of stay in neonatal intensive care unit (days)

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 15 Length of stay in neonatal intensive care unit (days)

Study	Interventionist N	Mean(SD)	Expectant N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
USA 1994	46	36.60 (17.40)	49	20.20 (14.00)		100.0	16.40 [10.02, 22.78]
Total (95% CI)	46		49			100.0	16.40 [10.02, 22.78]
Test for heterogeneity: not applicable							
Test for overall effect z=5.04 p<0.00001							

Analysis 01.16. Comparison 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia, Outcome 16 Gestation at birth (days)

Review: Interventionist versus expectant care for severe pre-eclampsia before term

Comparison: 01 Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia

Outcome: 16 Gestation at birth (days)

Study	Interventionist N	Mean(SD)	Expectant N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
South Africa 1990	20	211.00 (15.00)	18	223.00 (13.00)		24.6	-12.00 [-20.90, -3.10]
USA 1994	46	216.00 (14.00)	49	233.00 (11.00)		75.4	-17.00 [-22.08, -11.92]
Total (95% CI)	66		67			100.0	-15.77 [-20.19, -11.36]
Test for heterogeneity chi-square=0.91 df=1 p=0.34 I^2 =0.0%							
Test for overall effect z=7.00 p<0.00001