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Plasma volume expansion for treatment of pre-eclampsia (Review)

Duley L, Williams J, Henderson-Smart DJ

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[Intervention Review]

Plasma volume expansion for treatment of pre-eclampsia

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ABSTRACT

Background

Plasma volume is reduced amongst women with pre-eclampsia. This association has led to the suggestion that expanding the plasma volume might improve maternal and uteroplacental circulation, and so potentially improve outcome for both the woman and her baby.

Objectives

The aim of this review was to assess the effects of plasma volume expansion for the treatment of women with pre-eclampsia.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register and the Cochrane Controlled Trials Register Issue 4, 2000 were searched for trials meeting the selection criteria.

We updated the search of the Cochrane Pregnancy and Childbirth Group's Trials Register on 1 October 2009 and added the results to the awaiting classification section.

Selection criteria

Randomised trials were included. Quasi-random designs were excluded. Participants were women with hypertension during pregnancy, with or without proteinuria. Women who were postpartum at trial entry were excluded. Interventions were any comparison of plasma volume expansion with no expansion, or of one plasma volume expander with another.

Data collection and analysis

Data were extracted independently by two reviewers. Discrepancies were resolved by discussion. There was no blinding of authorship or results.

Main results

Three trials involving 61 women were included in this review. All compared a colloid solution with no plasma volume expansion. For every outcome reported, the confidence intervals are very wide and cross the no effect line.

Authors' conclusions

There is insufficient evidence for any reliable estimates of the effects of plasma volume expansion for women with pre-eclampsia.

[Note: The 14 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

PLAIN LANGUAGE SUMMARY

Plasma volume expansion for treatment of pre-eclampsia

Not enough evidence to show the effects of plasma volume expansion for women with pre-eclampsia.

Blood plasma volume increases gradually in women during the second half of pregnancy. The increase is usually greater for women with multiple pregnancies and less for those with small babies. Plasma volume is reduced in women with pre-eclampsia (pregnancy induced complication that includes high blood pressure). It is possible that women with pre-eclampsia might benefit from expanded plasma volume if it were to increase blood circulation for the mother and baby. The review of trials found there was not enough evidence to show the effects of plasma volume expansion for women with pre-eclampsia. More research is needed.

BACKGROUND

During normal pregnancy there are considerable changes in blood pressure. Within the first weeks the woman's blood pressure falls, largely due to a general relaxation of muscles within the blood vessels (Hytten 1980). From around the middle of pregnancy it rises slowly again until, at term, blood pressure is close to the level it was before pregnancy. Blood pressure during pregnancy can be influenced by many other factors, however, including time of day, physical activity, position and anxiety. High blood pressure alone has little effect on the outcome of pregnancy, but rises in blood pressure may be associated with other complications. Of these, the most common is pre-eclampsia. This is a multisystem disorder of pregnancy which commonly presents with raised blood pressure and proteinuria (Roberts 1993), and occurs in between 2-8% of pregnancies (WHO 1988). Although the outcome for most of these pregnancies is good, women with pre-eclampsia have an increased risk of developing serious problems, such as kidney failure, liver failure, abnormalities of the clotting system, stroke, premature birth (birth before 37 completed weeks), stillbirth or death of the baby in the first few weeks of life (Redman 1993).

Plasma is the fluid portion of blood. It is composed of a mixture of many proteins in a crystalloid solution. The volume of maternal plasma increases progressively during the second half of pregnancy. The increase tends to be greatest for women with multiple pregnancies and least for those whose babies are small for gestational age (Redman 1984). Plasma volume is reduced amongst women with pre-eclampsia, and this reduction is associated with a low concentration of serum albumin (a type of protein). This association has led to the suggestion that, for women with pre-eclampsia, expanding the plasma volume might improve maternal and uteroplacental circulation (Redman 1984). This would only be worthwhile if it was reflected in clinically important improvement in outcome for both the woman and her baby. Women with hypertension alone do not have the same changes in plasma volume, and are therefore less likely to benefit from plasma expansion.

Early uncontrolled reports of plasma volume expansion suggested that such therapy might improve blood pressure control, reducing the need for additional antihypertensive drugs (Collins 1989). These reports advocated the intravenous infusion of colloid solutions, such as dextran and salt-poor albumin. These colloid solutions are of particles in a dispersion medium. More recently the use of crystalloid solutions have also been reported (Gallery 1993).

Although there is little information about current clinical practice, anecdotally the use of plasma volume expanders for pre-eclampsia seems to be increasing. Most clinicians reserve such therapy for women with severe pre-eclampsia. There is no consensus on the type of agent to use, nor the amount and duration of treatment. Careful clinical monitoring is essential during and after plasma volume expansion, and some of those who use large volumes of expanders (> 500 millilitre (ml)) advocate the use of invasive cardiovascular monitoring, such as Swan Ganz catheters, as well as central venous catheters. The invasive forms of monitoring involve placing catheters in the cardiac blood vessels or chambers, and have hazards of their own which should be considered when evaluating plasma expansion.

Two recent systematic reviews of plasma volume expansion for critically ill people who are not pregnant have raised concern about its effectiveness and safety. The first compared human albumin plasma expansion with no albumin and concluded that albumin increased the risk of death (Albumin 1999). The second compared colloid solutions with crystalloids for fluid resuscitation, and demonstrated an increased mortality associated with the use of colloids (Schierhout 1999). In the UK, these reviews have recently led to a recommendation by the Committee of the Safety of Medicine that the indication for the use of human albumin solutions should focus on the use of albumin to replace lost fluids, and that 'hypoalbuminaemia' in itself was not an appropriate indication. Although none of the trials included in these reviews involved pregnant women, there is an urgent need to review the effects of both colloid and crystalloid solutions for women with pre-eclampsia.

Antihypertensive and anticonvulsant drug therapies for women with severe pre-eclampsia are evaluated in other reviews (Duley 2001; Duley 2001a)

OBJECTIVES

To estimate the main effects for women and their babies of plasma volume expansion when used for the treatment of pre-eclampsia during pregnancy and labour.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials of plasma volume expansion for treatment of hypertension during pregnancy. Quasi-randomised trials were excluded.

Types of participants

Women with hypertension during pregnancy, whether or not proteinuria was specified to be present. Although the primary aim was to evaluate plasma volume expansion for women with pre-eclampsia (hypertension plus proteinuria), women with hypertension alone were not excluded.

Women who were postpartum at trial entry were excluded.

Types of interventions

Plasma volume expansion with either colloid or crystalloid solutions compared with no expansion. Also, comparisons of different types of plasma volume expansion.

Types of outcome measures

For the women: death, eclampsia; measures of serious maternal morbidity related to pre-eclampsia and plasma volume expansion (such as pulmonary oedema, renal failure, cardiac arrest, liver failure, stroke, and coagulopathy); need for antihypertensive drugs; caesarean section; use of health service resources (invasive monitoring, dialysis, ventilation, admission to intensive care, length of stay); women's views.

For the baby: perinatal and neonatal mortality; measures of serious neonatal morbidity (low Apgar scores, intraventricular haemorrhage); measures of infant and child development (such as cerebral palsy); use of health service resources (such as admission to special care nursery, ventilation, length of stay in hospital).

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 (22 December 2000). We updated this search on 1 October 2009 and added the results to Studies awaiting classification.

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

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

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

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

In addition, The Cochrane Controlled Trials Register (CCTR 2000) was searched using the search strategy in Appendix 1 (last search Issue 4, 2000).

We did not apply any language restrictions.

Data collection and analysis

Data were extracted by Lelia Duley and John Williams. There was no blinding of authorship or results. Discrepancies were resolved by discussion. A quality score for concealment of allocation was assigned to each trial, using the following criteria:

(A) adequate concealment of allocation;
(B) unclear whether adequate concealment of allocation;
(C) inadequate concealment of allocation.

Quasi-randomised studies were excluded.

In addition, outcomes were excluded from the review if data for more than 20% of participants were not reported.

RESULTS

Description of studies

These studies all used colloid solutions for plasma volume expansion. None used crystalloid solutions. The women in one study (South Africa 1989) all had severe proteinuric pre-eclampsia. In the other two studies proteinuria was not present for all women at trial entry, and women with severe hypertension were excluded (UK 1993; USA 1980).

All women in one study (South Africa 1989) had a Swan Ganz catheter. In this trial (South Africa 1989) all women received magnesium sulphate, in another use of magnesium sulphate was reported as an outcome (USA 1980).

Risk of bias in included studies

The trials included in this review were all very small, and none describe, in adequate detail, the method used to conceal the allocation to treatment group.

Effects of interventions

Three trials involving 61 women were included in this review. Most women had pre-eclampsia, but two studies also recruited some women with hypertension but no proteinuria. All studies compared a colloid solution with no plasma volume expansion.

Two trials reported data on 'use of additional therapy' and caesarean section. Other outcomes were reported in single studies only. For every outcome reported, the confidence intervals are wide and cross the no effect line. (Fourteen reports from an updated search in October 2009 have been added to Studies awaiting classification.)

DISCUSSION

This review includes a very small number of women. Two out of the three trials included some women with hypertension alone. These women are less likely to benefit from plasma volume expansion than women with pre-eclampsia. Future versions of this review may consider outcome for subgroups of women with different severity of disease, if there is any overall evidence of benefit.

Only two outcomes were reported by more than one of the three trials in the review. The confidence intervals for these two outcomes, 'use of additional therapy' and 'caesarean section' include everything from a halving in risk to a three times increase (relative risk (RR) 1.51, 95% confidence interval (CI) 0.73-3.11 and RR 1.46, 95% CI 0.75-2.85). This is insufficient evidence for any reliable estimates of the effects of plasma volume expansion for women with pre-eclampsia.

The trials in this review only evaluated colloid solutions. Data were not reported for many important outcomes, such as pulmonary oedema, renal failure, dialysis, admission to intensive care and perinatal morbidity. Even taken together, the studies included in this review are too small for any reliable conclusions about the overall effects of plasma volume expansion for women with pre-eclampsia. These data should also be considered alongside the evidence for critically ill non-pregnant people, for whom albumin, and possibly other colloids, increase mortality. Until further evidence becomes available, this suggests that colloid solutions should be used with considerable caution.

For crystalloid solutions, there are no reliable data from randomised trials on either their effectiveness or safety during pregnancy.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review are inconclusive about the effects of plasma volume expansion for treatment of women with pre-

eclampsia. There is a strong argument that the use of plasma volume expansion, especially colloid solutions, during pregnancy should be restricted to randomised trials.

Implications for research

The effectiveness and safety of colloid and crystalloid solutions when used for plasma volume expansion as treatment of pre-eclampsia can only be assessed in large randomised trials. Such trials should evaluate crystalloid solutions as, in non-pregnant people, these appear to be safer than colloid solutions. They have the added bonus of being considerably cheaper. Any such trials should probably be restricted to women with severe pre-eclampsia, as they have the most potential for benefit.

[Note: The 14 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

ACKNOWLEDGEMENTS

None.

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CHARACTERISTICS OF STUDIES

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

South Africa 1989

Methods	'Randomly allocated', no further information.

South Africa 1989 *(Continued)*

Participants	10 women with severe pre-eclampsia; BP > 160/110 mmHg and at least 1g/litre proteinuria. No pre-existing hypertension, renal disease, heart disease or antihypertensives. Not in labour. All women had a Swan Ganz catheter inserted.
Interventions	Expansion: 200 ml 3.5% haemaccel, then successive 200 ml over 30 minutes until pulmonary capillary wedge pressure increased by at least 16 mmHg. Then hydralazine 25 mg/200 ml infused to keep DBP 90-110 mmHg. Control: hydralazine as above, but without prior infusion.
Outcomes	Women: caesarean section, mean gestation, change in pulmonary wedge pressure, cardiac index and systemic vascular resistance. Baby: birthweight, Apgar at 1 and 5 minutes.
Notes	Four women had magnesium sulphate before entry, the others started it after hydralazine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

UK 1993

Methods	'Predetermined randomisation schedule', no further information.
Participants	15 women with PIH; SBP rise of 30 mmHg DBP rise of 15mmHg compared to BP before 20 weeks, twice at least six hours apart. Six women had proteinuria. Excluded if BP > 170/110 mmHg, chronic hypertension, cardiac or renal disease, or antihypertensive agent started.
Interventions	Expansion: haemaccel 500 ml over 25-30 minutes. Control: hypotonic saline 500 ml over 25-30 minutes.
Outcomes	Women: antihypertensive therapy, mean blood pressure changes, median delay to delivery, changes in various haematological measures. Baby: none.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

USA 1980

Methods	'Randomly assigned by blind draw' into three groups, no further information. Three women delivered and one withdrew before treatment.
Participants	36 primiparous women with pre-eclampsia, defined as hypertension plus proteinuria and/or oedema. Age 15-33, gestation 28-40 weeks. Excluded if cardiac disease, renal or pulmonary insufficiency, severe pre-eclampsia (if required antihypertensive drugs and prompt delivery).

USA 1980 *(Continued)*

Interventions	Expansion: (a) plasmanate 500 ml over eight hours day one, 250 ml over four hours day two (b) dextran 40 1000 ml over eight hours day one, 500 ml over four hours day two. Control: 5% dextrose in distilled water 1000 ml over eight hours day one, 500ml over four hours day two. Treatment started after 24 hours assessment, with bed rest, sedatives and magnesium sulphate as indicated.
Outcomes	Women: use of magnesium sulphate, caesarean section, preterm delivery, placental abruption, change in urine output and haematocrit. Baby: death.
Notes	Twins mentioned in the text, but not clear how many and in which group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

BP=blood pressure; DBP=diastolic blood pressure; mg=milligram; ml=millilitre; mmHg=millimeter of mercury; PIH=pregnancy induced hypertension; SBP=systolic blood pressure

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

Study	Reason for exclusion
Denmark 1984	Case series, no control group. Participants: 14 women with pre-eclampsia. Intervention: plasma volume expansion with albumin (100 ml/hr), plus sedation and antihypertensive drugs.
Germany 1993	The women did not have pre-eclampsia and no clinical outcomes reported. Study design: double blind randomised. Participants: 12 women with haemoconcentration (Hb > 13g/dl).
Netherlands 1992	Not a randomised trial. Available as an abstract only. Participants: 14 women with absent or reversed end diastolic flow in the umbilical artery. Interventions: Plasma volume expansion versus bed rest and antihypertensive drugs.
South Africa 1988	Quasi-randomised trial, every third women used as a control. No outcomes reported. Participants: 21 women with DBP 90-119 mmHg, and > 20 weeks gestation. Interventions: human serum 500 ml over 90 minutes versus no volume expansion.
UK 1986	Published as an abstract only. 'Randomly allocated' no further information. No clinical outcomes reported. Participants: 15 women with severe pre-eclampsia. Intervention: 100mg salt poor albumin by intravenous infusion until delivery.
USA 1989	Quasi randomised trial. Registered as an ongoing study in 1987, and said by author to have been completed in 1989. Participants: 62 women with pre-eclampsia prior to delivery, < 37 weeks gestation. Intervention: 4 different ways for rapidly expanding plasma volume.

Study	Reason for exclusion
	Outcomes: No clinical outcomes, laboratory results only.

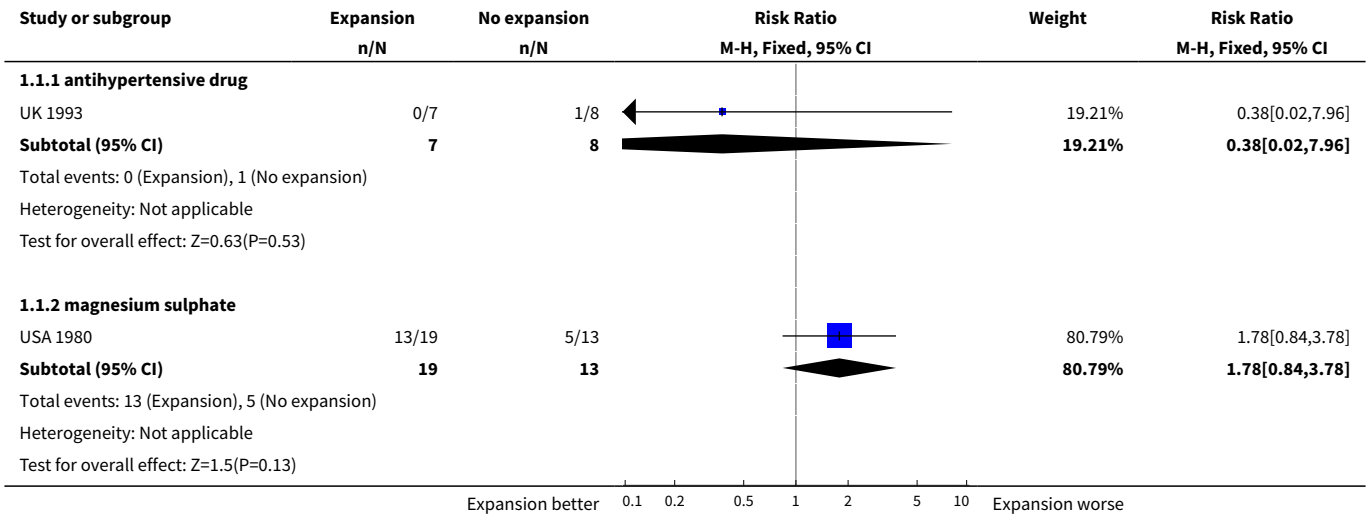
DBP=diastolic blood pressure; hr=hour; ml=millilitre; mmHg=millimeter of mercury

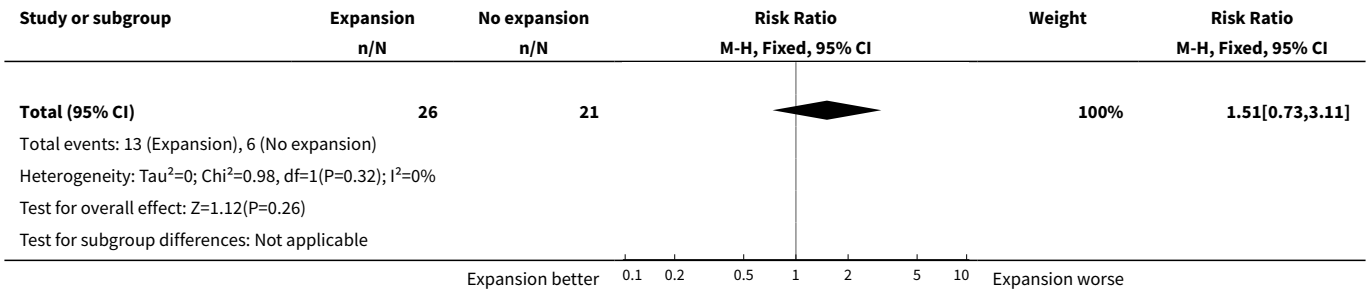
DATA AND ANALYSES

Comparison 1. Plasma volume expansion versus no expansion

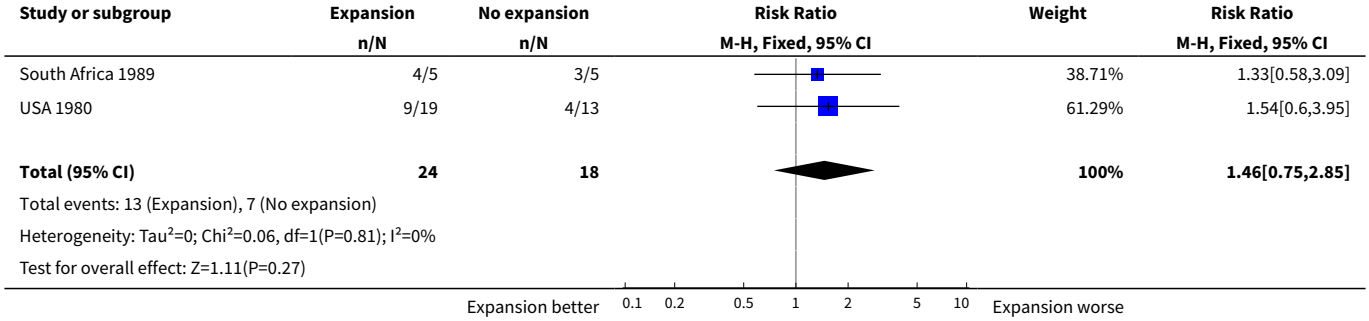
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 use of additional drug therapy	2	47	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.73, 3.11]
1.1 antihypertensive drug	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 7.96]
1.2 magnesium sulphate	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.84, 3.78]
2 caesarean section	2	42	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.75, 2.85]
4 placental abruption	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.14, 13.57]
5 preterm delivery	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.42, 4.51]
6 perinatal death	1	32	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [0.18, 67.45]
7 birthweight < 2500 g	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.77, 3.22]
8 Apgar at 5 minutes < 7	1	10	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.45, 19.93]

Analysis 1.1. Comparison 1 Plasma volume expansion versus no expansion, Outcome 1 use of additional drug therapy.

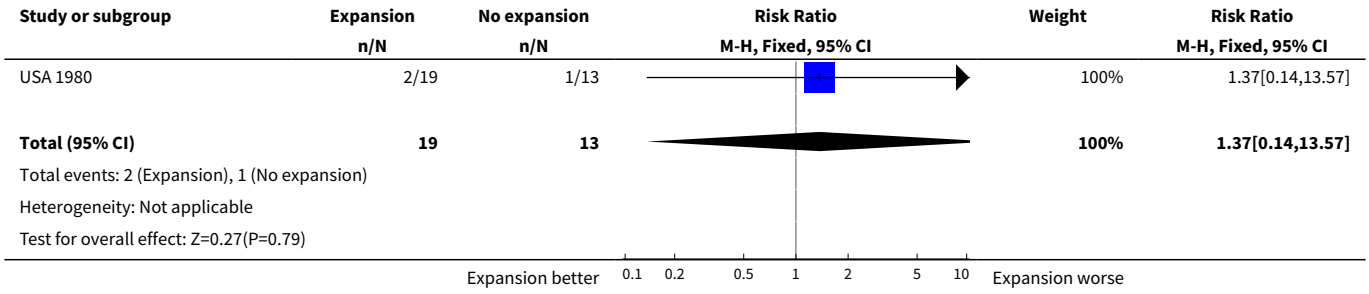




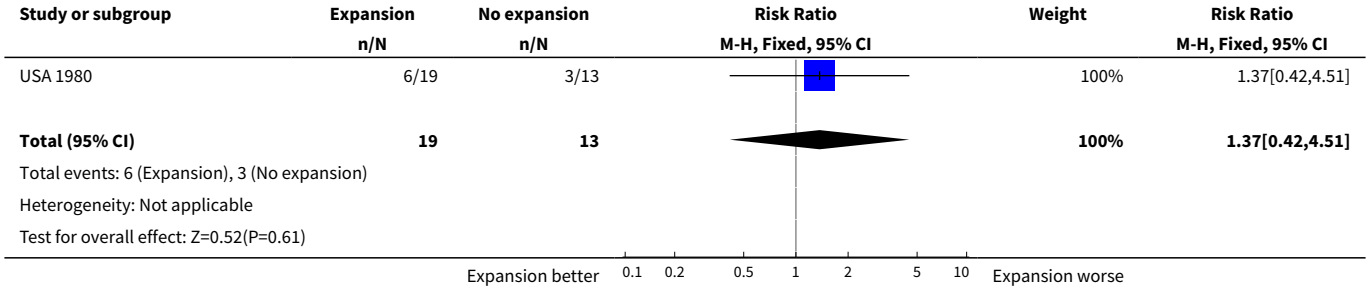
Analysis 1.2. Comparison 1 Plasma volume expansion versus no expansion, Outcome 2 caesarean section.



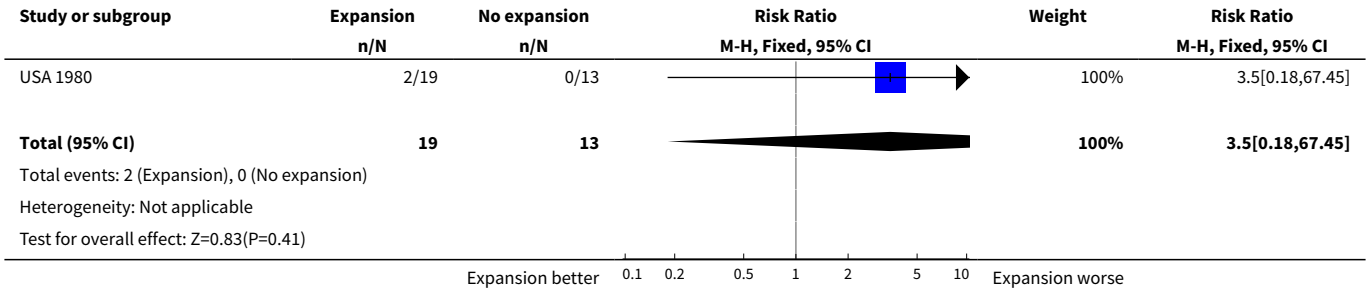
Analysis 1.4. Comparison 1 Plasma volume expansion versus no expansion, Outcome 4 placental abruption.



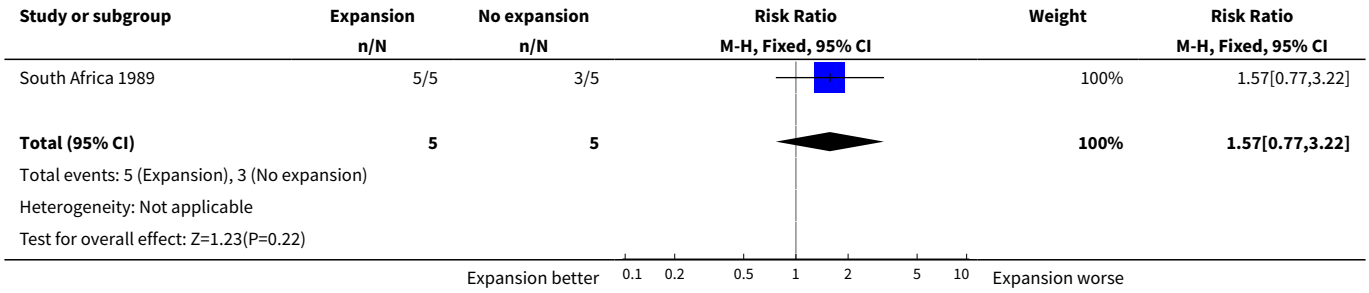
Analysis 1.5. Comparison 1 Plasma volume expansion versus no expansion, Outcome 5 preterm delivery.



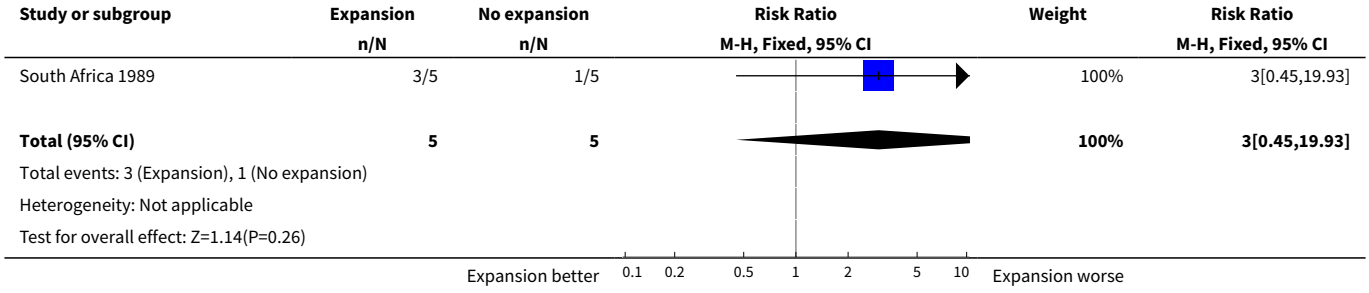
Analysis 1.6. Comparison 1 Plasma volume expansion versus no expansion, Outcome 6 perinatal death.



Analysis 1.7. Comparison 1 Plasma volume expansion versus no expansion, Outcome 7 birthweight < 2500 g.



Analysis 1.8. Comparison 1 Plasma volume expansion versus no expansion, Outcome 8 Apgar at 5 minutes < 7.



APPENDICES

Appendix 1. Search strategy

1. PLASMA-VOLUME*:ME
2. (PLASMA next VOLUME)
3. EXPAN*
4. (#1 or #2)
5. (#3 and #4)
6. (PLASMA next EXPAN*)

7. PLASMA-SUBSTITUTES*:ME
8. ALBUMIN
9. (#5 or #6 or #7 or #8)
10. PREGNANCY-TOXEMIAS*:ME
11. PREECLAMP*
12. PRE-ECLAMP*
13. (PRE next ECLAMP*)
14. ECLAMP*
15. (HYPERTENS* and PREGNAN*)
16. (((((#10 or #11) or #12) or #13) or #14) or #15)
17. (#16 and #9)

WHAT'S NEW

Date	Event	Description
1 October 2009	Amended	Search updated. Fourteen reports added to Studies awaiting classification.

HISTORY

Protocol first published: Issue 4, 1999
Review first published: Issue 4, 1999

Date	Event	Description
20 September 2008	Amended	Converted to new review format.
25 July 2001	New search has been performed	Two new excluded studies added, UK 1986 and Germany 1993.

CONTRIBUTIONS OF AUTHORS

Methods were developed and agreed by all three reviewers. Lelia Duley and John Williams checked for potentially eligible studies and extracted the data. Lelia Duley entered the data and drafted the text of the review, with comments and input from David Henderson-Smart and John Williams.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- NSW Centre for Perinatal Health Services Research, University of Sydney, Australia.
- Countess of Chester Hospital NHS Trust, UK.
- Resource Centre for Randomised Trials, Oxford, UK.

External sources

- Medical Research Council, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Plasma Substitutes [*therapeutic use]; Pre-Eclampsia [*therapy]

MeSH check words

Female; Humans; Pregnancy