Cochrane
Library

Cochrane Database of Systematic Reviews

Acute tocolysis for uterine tachysystole or suspected fetal distress (Review)

Leathersich SJ, Vogel JP, Tran TS, Hofmeyr GJ

Leathersich SJ, Vogel JP, Tran TS, Hofmeyr GJ.
Acute tocolysis for uterine tachysystole or suspected fetal distress.
Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD009770.
DOI: [10.1002/14651858.CD009770.pub2](https://doi.org/10.1002/14651858.CD009770.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	3
SUMMARY OF FINDINGS	4
BACKGROUND	15
OBJECTIVES	16
METHODS	16
RESULTS	19
Figure 1.	20
Figure 2.	22
Figure 3.	23
DISCUSSION	28
AUTHORS' CONCLUSIONS	29
ACKNOWLEDGEMENTS	30
REFERENCES	31
CHARACTERISTICS OF STUDIES	34
DATA AND ANALYSES	48
Analysis 1.1. Comparison 1 Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 1 Fetal or neonatal mortality.	49
Analysis 1.2. Comparison 1 Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 2 Five-minute Apgar score < 7.	49
Analysis 1.3. Comparison 1 Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 3 Fetal heart rate tracing not improved.	49
Analysis 2.1. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 1 Perinatal death or severe morbidity.	50
Analysis 2.2. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 2 Fetal or neonatal mortality.	50
Analysis 2.3. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 3 Caesarean delivery.	51
Analysis 2.4. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 4 Five-minute Apgar score < 7.	51
Analysis 2.5. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 5 Umbilical artery pH.	51
Analysis 2.6. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 6 Abnormal fetal heart rate tracing.	51
Analysis 2.7. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 7 Maternal side effects (tachycardia or palpitations).	52
Analysis 2.8. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 8 Admission to NICU.	52
Analysis 3.1. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 1 Caesarean delivery.	53
Analysis 3.2. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 2 Five-minute Apgar score < 7.	53
Analysis 3.3. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 3 Umbilical artery pH < 7.1.	53
Analysis 3.4. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 4 Umbilical cord blood base excess < -12.	54
Analysis 3.5. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 5 Admission to NICU.	54
Analysis 4.1. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 1 Fetal or neonatal mortality.	55
Analysis 4.2. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 2 Five-minute Apgar score < 7.	55
Analysis 4.3. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 3 Umbilical artery pH < 7.2.	55
Analysis 4.4. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 4 Fetal heart rate tracing not improved.	56
Analysis 4.5. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 5 Meconium-stained amniotic fluid.	56
Analysis 4.6. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 6 Umbilical cord blood base excess < -10.	56
Analysis 4.7. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 7 Admission to NICU.	57
Analysis 5.1. Comparison 5 Subcutaneous terbutaline versus IV magnesium sulphate, Outcome 1 Umbilical artery pH < 7.2.	57
Analysis 5.2. Comparison 5 Subcutaneous terbutaline versus IV magnesium sulphate, Outcome 2 Resolution of fetal distress on fetal heart rate tracing.	57

Analysis 6.1. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 1 Caesarean delivery.	58
Analysis 6.2. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 2 Five-minute Apgar score < 7.	58
Analysis 6.3. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 3 Umbilical artery pH < 7.0.	59
Analysis 6.4. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 4 Time to resolution of uterine hyperstimulation.	59
Analysis 6.5. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 5 Recurrence of hyperstimulation after initial resolution.	59
Analysis 7.1. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 1 Fetal or neonatal mortality.	60
Analysis 7.2. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 2 Five-minute Apgar score < 7.	60
Analysis 7.3. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 3 Umbilical artery pH.	61
Analysis 7.4. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 4 Abnormal FHR.	61
Analysis 7.5. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 5 No improvement in FHR.	61
Analysis 8.1. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 1 Caesarean delivery.	62
Analysis 8.2. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 2 Five-minute Apgar score < 7.	62
Analysis 8.3. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 3 Umbilical artery pH < 7.0.	63
Analysis 8.4. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 4 Uterine tachysystole 10 minutes after drug.	63
Analysis 8.5. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 5 Need for repeat dose of tocolytic.	63
Analysis 8.6. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 6 Successful fetal intrauterine resuscitation.	63
Analysis 8.7. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 7 Meconium-stained amniotic fluid.	64
Analysis 8.8. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 8 Admission to NICU.	64
Analysis 8.9. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 9 Postpartum haemorrhage.	64
APPENDICES	65
CONTRIBUTIONS OF AUTHORS	65
DECLARATIONS OF INTEREST	65
SOURCES OF SUPPORT	65
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	65
INDEX TERMS	66

[Intervention Review]

Acute tocolysis for uterine tachysystole or suspected fetal distress

Sebastian J Leathersich¹, Joshua P Vogel², Thach Son Tran³, G Justus Hofmeyr⁴

¹King Edward Memorial Hospital for Women, Subiaco, Australia. ²UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland. ³Clinical Studies and Epidemiology, Bone Biology Division, Garvan Institute of Medical Research, Darlinghurst, Australia. ⁴Walter Sisulu University, University of the Witwatersrand, Eastern Cape Department of Health, East London, South Africa

Contact: Sebastian J Leathersich, King Edward Memorial Hospital for Women, 374 Bagot Road, Subiaco, WA, 6008, Australia. sebastian.leathersich@health.wa.gov.au, sebastian.leathersich@gmail.com.

Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: New, published in Issue 7, 2018.

Citation: Leathersich SJ, Vogel JP, Tran TS, Hofmeyr GJ. Acute tocolysis for uterine tachysystole or suspected fetal distress. *Cochrane Database of Systematic Reviews* 2018, Issue 7. Art. No.: CD009770. DOI: [10.1002/14651858.CD009770.pub2](https://doi.org/10.1002/14651858.CD009770.pub2).

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Uterine tachysystole (more than 5 contractions per 10 minutes in 2 consecutive intervals) is common during labour, particularly with use of labour-stimulating agents. Tachysystole may reduce fetal oxygenation by interrupting maternal blood flow to the placenta during contractions. Reducing uterine contractions may improve placental blood flow, improving fetal oxygenation. This review aimed to evaluate the use of tocolytics to reduce or stop uterine contractions for improvement of the condition of the fetus in utero. This new review supersedes an earlier Cochrane Review on the same topic.

Objectives

To assess the effects of the use of acute tocolysis during labour for uterine tachysystole or suspected fetal distress, or both, on fetal, maternal and neonatal outcomes.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register, [ClinicalTrials.gov](https://www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (2 February 2018), and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs) evaluating acute tocolysis for uterine tachysystole, intrapartum fetal distress, or both.

Data collection and analysis

We used standard methods expected by Cochrane.

Main results

We included eight studies (734 women), conducted in hospital settings, predominantly in high-income countries (USA, Austria, Uruguay). Two trials were conducted in upper and lower middle-income countries (South Africa, Sri Lanka). The hospital facilities all had the capacity to perform caesarean section. Overall, the studies had a low risk of bias, except for methods to maintain blinding. All of the trials used a selective beta₂ (β₂)-adrenergic agonist in one arm, however the drug used varied, as did the comparator. Limited information was available on maternal outcomes.

Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery

There were two stillbirths, both in the no tocolytic control group (risk ratio (RR) 0.23, 95% confidence interval (CI) 0.01 to 4.55; 2 studies, 57 women; low-quality evidence). One had gross hydrocephalus and the second occurred with vaginal delivery after waiting 55 minutes for caesarean section. The decision for caesarean section delivery was an inclusion criterion in both studies so we could not assess this as an outcome under this comparison. Abnormal fetal heart trace is probably lower with tocolytic treatment (RR 0.28, 95% CI 0.08 to 0.95; 2 studies, 43 women; moderate-quality evidence). The effects on the number of babies with Apgar score below seven were uncertain (low-quality evidence).

Intravenous (IV) atosiban versus IV hexoprenaline (1 study, 26 women)

One infant in the hexoprenaline group required > 24 hours in the neonatal intensive care unit (NICU) following a forceps delivery (RR 0.33, 95% CI 0.01 to 7.50; low-quality evidence). There were no fetal or neonatal mortalities and no Apgar scores below seven. There was one caesarean delivery in the IV hexoprenaline group (RR 0.33, 95% CI 0.01 to 7.50; low-quality evidence), and one case of abnormal fetal heart score in the atosiban group (RR 3.00, 95% CI 0.13 to 67.51; very low-quality evidence).

IV fenoterol bromhydrate versus emergency delivery (1 study, 390 women)

No data were reported for perinatal death, severe morbidity or fetal or neonatal mortality. IV fenoterol probably increases the risk of caesarean delivery (RR 1.12, 95% CI 1.04 to 1.22; moderate-quality evidence). Fenoterol may have little or no effect on the risk of Apgar scores below seven (RR 1.28, 95% CI 0.35 to 4.68; low-quality evidence).

IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery (1 study, 37 women)

No data were reported for perinatal death or severe morbidity. There were two fetal deaths in the no tocolytic control group (RR 0.23, 95% CI 0.01 to 4.55; low-quality evidence). The rate of caesarean delivery was not reported. There were two babies with Apgar scores below seven in the control group and none in the hexoprenaline group (RR 0.24, 95% CI 0.01 to 4.57; 35 women; low-quality evidence).

Subcutaneous terbutaline versus IV magnesium sulphate (1 study, 46 women)

No data were reported for perinatal death, severe morbidity or fetal or neonatal mortality. The decision for caesarean section was an inclusion criterion, so we could not assess this. The effects on abnormal fetal heart trace are uncertain (very low-quality evidence).

Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic agent (1 study, 28 women)

No data were reported for perinatal death, severe morbidity or fetal or neonatal mortality. There may be little or no difference in the rates of caesarean delivery in the subcutaneous terbutaline (8/15) and control groups (4/13) (RR 1.73, 95% CI 0.68 to 4.45; low-quality evidence). There were no cases of Apgar scores below seven or abnormal fetal heart trace.

Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery (1 study, 20 women)

No data were reported for perinatal death or severe morbidity. There were no fetal or neonatal mortalities. The decision for caesarean section was an inclusion criterion, so we could not assess this. There were two babies with Apgar scores below seven in the control group and none in the terbutaline group (RR 0.17, 95% CI 0.01 to 3.08; low-quality evidence).

IV terbutaline versus IV nitroglycerin (1 study, 110 women)

No data were reported for perinatal death or severe morbidity or fetal or neonatal mortality. There may be little or no difference in the rates of caesarean delivery between the IV terbutaline (30/57) and control groups (29/53) (RR 0.96, 95% CI 0.68 to 1.36; low-quality evidence). There were no cases of Apgar scores below seven.

Authors' conclusions

There is insufficient evidence to determine the effects of tocolytics for uterine tachysystole or suspected fetal distress during labour. The clinical significance for some of the improvements in measures of fetal well-being with tocolytics is unclear. The sample sizes were too small to detect effects on neonatal morbidity, mortality or serious adverse effects. The majority of studies are from high-income countries in facilities with access to caesarean section, which may limit the generalisability of the results to lower-resource settings, or settings where caesarean section is not available.

Further well-designed and adequately powered RCTs are required to evaluate clinically relevant indicators of maternal and neonatal morbidity and mortality.

PLAIN LANGUAGE SUMMARY

Medications for reducing contractions during labour for excessively strong/frequent contractions or where the unborn baby is thought to be distressed

What is the issue?

Excessively strong or frequent contractions can occur in any labour, though are more common when women have been given medications to start off or increase contractions. In some cases, excessive contractions can be a sign of complications such as placental abruption or obstructed labour. Excessive contractions may reduce the amount of oxygen reaching the unborn baby.

'Tocolysis' is when women are given medication to reduce the strength or frequency of contractions, or both. Tocolysis may improve blood flow and therefore improve the baby's well-being. This review aimed to evaluate the benefits and harms of tocolysis when the uterus (womb) is contracting too quickly (more than 5 contractions in 2 consecutive 10-minute periods) or when the baby is showing signs of distress during labour, as detected by monitoring its heart rate.

This new Cochrane Review supersedes an earlier Cochrane Review with the same name.

Why is this important?

Babies who are deprived of oxygen during labour can develop serious problems, including cerebral palsy, organ damage or death. When fetal monitoring suggests fetal distress, measures can be taken to improve the baby's oxygen levels. This can include the use of tocolytic medications. This may be particularly important in low-resource environments, where an emergency delivery or caesarean section may not be immediately available.

What evidence did we find?

We searched for evidence in February 2018 and found eight randomised controlled trials (involving 734 women) who had excessive uterine contractions, signs of fetal distress, or both during labour. The trials tested different comparison groups, which means that our analyses were based on data from single studies involving small numbers of women. Women were randomised to receiving a β_2 -adrenergic tocolytic drug or an alternative approach (including no tocolytic while awaiting caesarean section, stopping medications that increase contraction strength, or using a different tocolytic such as atosiban, magnesium sulphate or nitroglycerin).

We combined data from two small trials (57 women), comparing a β_2 -adrenergic tocolytic drug with no tocolytic drug. Two babies died in their mother's womb, both occurring in the group of women who did not receive a tocolytic - one had gross hydrocephalus (too much fluid in and around the brain) and the other occurred whilst the mother was waiting to have a caesarean section. The number of babies with an abnormal fetal heart rate is probably lower in the group of women who were given a tocolytic, but the effects on other measures of infant well-being were uncertain.

Very few serious side effects were found, but the studies were too small to assess uncommon adverse effects.

It is not possible to draw clear conclusions about the benefits and harms and the quality of the evidence was very low to moderate.

What does this mean?

There is not enough evidence from randomised controlled trials to determine the effects of tocolysis for women with fetal distress or excessive uterine contractions, nor to identify whether one type of tocolytic drug is safer or more effective than another.

The clinical significance for some of improvements in measures of fetal well-being with tocolytics is unclear. Generally, sample sizes were too small to detect effects on maternal or infant well-being or serious adverse effects. The majority of studies were from high-income countries in healthcare facilities with access to caesarean section, which may limit the applicability of these results to lower-resource settings, or settings where caesarean section is not available.

Further high-quality studies, involving large numbers of women, are needed. Such studies could focus on measuring clinically relevant outcomes for the mother and her baby such as death of the mother, her baby, and other measures of well-being and safety.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings for selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery

Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery for the management of intrapartum fetal distress

Patient or population: women with fetal distress for whom the decision had been made to delivery by emergency caesarean section

Setting: hospitals with the capacity for caesarean section in South Africa or the United States

Intervention: β_2 -adrenergic receptor agonist whilst awaiting emergency delivery

Comparison: no tocolytic whilst awaiting emergency delivery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no tocolytic agent whilst awaiting emergency delivery	Risk with β_2 -adrenergic receptor agonist whilst awaiting emergency delivery				
Perinatal death or severe morbidity	No data available					
Fetal or neonatal mortality	Study population		RR 0.23 (0.01 to 4.55)	57 (2 RCTs)	⊕⊕⊕⊖ LOW 1,2	
	69 per 1000	16 per 1000 (1 to 314)				
Caesarean delivery	No data available					Caesarean delivery was an inclusion criteria for both trials
5-minute Apgar score < 7	Study population		RR 0.20 (0.02 to 1.57)	55 (2 RCTs)	⊕⊕⊕⊖ LOW 1,2	
	143 per 1000	29 per 1000 (3 to 224)				
Low umbilical artery pH (less than 7.0 or as defined by trial authors)						No trial reported this outcome
Abnormal FHR as defined by trial authors (FHR tracing not improved)	Study population		RR 0.28 (0.08 to 0.95)	43 (2 RCTs)	⊕⊕⊕⊖ MODERATE 2	
	947 per 1000	265 per 1000				

(133 to 521)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FHR:** fetal heart rate; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Wide confidence interval crossing the line of no effect (-1).

²Small sample size (-1).

Summary of findings 2. Summary of findings for IV atosiban versus IV hexoprenaline

IV atosiban versus IV hexoprenaline for the management of intrapartum fetal distress

Patient or population: women with severe intrapartum fetal bradycardia

Setting: Austrian hospital with capacity for caesarean section

Intervention: IV atosiban (6.75 mg)

Comparison: IV hexoprenaline (5 µg)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with IV hexoprenaline	Risk with IV atosiban				
Perinatal death or severe morbidity	Study population		RR 0.33 (0.01 to 7.50)	26 (1 RCT)	⊕⊕⊕⊖ LOW ^{1 2}	
	77 per 1000	25 per 1000 (1 to 577)				
Fetal or neonatal mortality	Study population		Not estimable	26 (1 RCT)	⊕⊕⊕⊖ LOW ^{1 3}	
	0 per 1000	0 per 1000 (0 to 0)				
Caesarean delivery	Study population		RR 0.33 (0.01 to 7.50)	26 (1 RCT)	⊕⊕⊕⊖ LOW ^{1 2}	
	77 per 1000	25 per 1000				

	(1 to 577)				
5-minute Apgar score < 7	Study population		Not estimable	26 (1 RCT)	⊕⊕⊕⊕ LOW ^{1 3}
	0 per 1000	0 per 1000 (0 to 0)			
Umbilical artery pH	The mean umbilical artery pH was 7.2	The mean difference in umbilical artery pH in the intervention group was 0 (0.05 fewer to 0.05 more)	-	26 (1 RCT)	⊕⊕⊕⊕ LOW ^{1 2}
Abnormal FHR tracing	Study population		RR 3.00 (0.13 to 67.51)	26 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2 3}
	0 per 1000	0 per 1000 (0 to 0)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FHR:** fetal heart rate; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Small sample size (-1).

²Wide confidence interval crossing the line of no effect (-1).

³Few/no events (-1).

Summary of findings 3. Summary of findings for IV fenoterol bromhydrate versus emergency delivery

IV fenoterol versus emergency delivery for the management of intrapartum fetal distress

Patient or population: women with a non-reassuring fetal heart trace during labour but without uterine tachysystole

Setting: hospital in Uruguay with capacity for caesarean section

Intervention: IV fenoterol bromhydrate (0.1 mg/minute, titrated according to response)

Comparison: emergency delivery

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	Nº of participants	Quality of the evidence	Comments
----------	--	--------------------------	--------------------	-------------------------	----------

	Risk with emer- gency delivery	Risk with IV fenoterol bromhy- drate	(studies)		(GRADE)
Perinatal death or severe morbidity	No data available				
Fetal or neonatal mortality	No data available				
Caesarean delivery	Study population		RR 1.12 (1.04 to 1.22)	390 (1 RCT)	⊕⊕⊕⊖ MODERATE ¹
	807 per 1000	904 per 1000 (839 to 985)			
5-minute Apgar score < 7	Study population		RR 1.28 (0.35 to 4.68)	390 (1 RCT)	⊕⊕⊖⊖ LOW ^{1 2}
	20 per 1000	26 per 1000 (7 to 95)			
Umbilical artery pH < 7.1	Study population		RR 0.68 (0.44 to 1.05)	390 (1 RCT)	⊕⊕⊖⊖ LOW ^{1 2}
	213 per 1000	145 per 1000 (94 to 224)			
Abnormal FHR tracing	No data available				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FHR:** fetal heart rate; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Participants, clinicians and assessors were not blinded. There were risks identified for reporting bias (-1).

²Confidence interval crossing the line of no effect (-1).

Summary of findings 4. Summary of findings for IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery

IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, for the management of intrapartum fetal distress

Patient or population: women for whom a decision had been made to deliver by caesarean section for suspected fetal distress based on FHR monitoring

Setting: hospital in South Africa with capacity for caesarean section

Intervention: IV hexoprenaline (10 µg) whilst awaiting emergency delivery

Comparison: no tocolytic whilst awaiting emergency delivery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no tocolytic whilst awaiting emergency delivery	Risk with IV hexoprenaline				
Perinatal death or severe morbidity	No data available					
Fetal or neonatal mortality	Study population		RR 0.23 (0.01 to 4.55)	37 (1 RCT)	⊕⊕⊕⊕ LOW 1 2	
	100 per 1000	23 per 1000 (1 to 455)				
Caesarean delivery	No data available					
5-minute Apgar score < 7	Study population		RR 0.24 (0.01 to 4.57)	35 (1 RCT)	⊕⊕⊕⊕ LOW 1 2	
	105 per 1000	25 per 1000 (1 to 481)				
Umbilical artery pH < 7.2	Study population		RR 0.64 (0.30 to 1.35)	33 (1 RCT)	⊕⊕⊕⊕ LOW 1 2	
	588 per 1000	376 per 1000 (176 to 794)				
FHR tracing not improved	Study population		RR 0.43 (0.21 to 0.88)	23 (1 RCT)	⊕⊕⊕⊕ MODERATE 1	Non-prespecified. See Differences between protocol and review
	900 per 1000	387 per 1000 (189 to 792)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; FHR: fetal heart rate; RCT: randomised controlled trial; RR: risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Small sample size (-1).

²Wide confidence interval crossing the line of no effect (-1).

Summary of findings 5. Summary of findings for subcutaneous terbutaline versus IV magnesium sulphate

Subcutaneous terbutaline versus IV magnesium sulphate for the management of intrapartum fetal distress

Patient or population: women with intrapartum fetal distress for whom the decision had been made to deliver by caesarean section

Setting: hospital in the USA with capacity for caesarean section

Intervention: subcutaneous terbutaline (250 µg) followed by caesarean section within 15 minutes

Comparison: IV magnesium sulphate (4 g) followed by caesarean section within 15 minutes

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with IV magnesium sulphate	Risk with subcutaneous terbutaline				
Perinatal death or severe morbidity	No data available					
Fetal or neonatal mortality	No data available					
Caesarean delivery	No data available					
5-minute Apgar score < 7	No data available					
Umbilical artery pH < 7.2	Study population		RR 0.29 (0.07 to 1.23)	46 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2 3}	
	304 per 1000	88 per 1000 (21 to 374)				
Resolution of fetal distress on FHR tracing	Study population		RR 1.31 (0.97 to 1.77)	46 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2 3}	Non-prespecified. See Differences between
	696 per 1000	911 per 1000 (675 to 1000)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FHR:** fetal heart rate; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Participants, clinicians and assessors unblinded (-1).

²Small sample size (-1).

³Confidence interval crossing the line of no effect (-1).

Summary of findings 6. Summary of findings for subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic agent

Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic agent for the management of uterine hyperstimulation

Patient or population: women who developed uterine hyperstimulation in labour with oxytocin augmentation, but without signs of fetal distress

Setting: hospital in the USA with capacity for caesarean section

Intervention: subcutaneous terbutaline (250 µg, up to 3 doses 15 minutes apart) with continuation of the oxytocin infusion

Comparison: cessation of the oxytocin infusion without administration of a tocolytic

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with cessation of oxytocic infusion without tocolytic	Risk with subcutaneous terbutaline with continuation of oxytocic				
Perinatal death or severe morbidity	No data available					
Fetal or neonatal mortality	No data available					

Caesarean delivery	Study population		RR 1.73 (0.68 to 4.45)	28 (1 RCT)	⊕⊕⊕⊖ LOW ^{1 2}
	308 per 1000	532 per 1000 (209 to 1000)			
5-minute Apgar score < 7	Study population		Not estimable	28 (1 RCT)	⊕⊖⊖⊖ VERY LOW ^{1 3 4}
	0 per 1000	0 per 1000 (0 to 0)			
Umbilical artery pH < 7.0	Study population		Not estimable	28 (1 RCT)	⊕⊖⊖⊖ VERY LOW ^{1 3 4}
	0 per 1000	0 per 1000 (0 to 0)			
Abnormal FHR tracing	No data available				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹No blinding of participants, clinicians or assessors (-1).

²Confidence interval crossing the line of no effect (-1).

³No events in either group (-1).

⁴Small sample size (-1).

Summary of findings 7. Summary of findings for subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery

Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, for the management of intrapartum fetal distress

Patient or population: women in labour with signs of fetal distress and a fetal scalp pH < 7.25, for whom the decision had been made for emergency delivery

Setting: hospital in the USA with capacity for caesarean section

Intervention: subcutaneous terbutaline (250 µg) whilst awaiting emergency delivery

Comparison: no tocolytic whilst awaiting emergency delivery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no tocolytic whilst awaiting emergency delivery	Risk with subcutaneous terbutaline				
Perinatal death or severe morbidity	No data available					
Fetal or neonatal mortality	Study population		Not estimable	20 (1 RCT)	⊕⊕⊕⊕ LOW 2 3	
	0 per 1000	0 per 1000 (0 to 0)				
Caesarean delivery	No data available					
5-minute Apgar score < 7	Study population		RR 0.17 (0.01 to 3.08)	20 (1 RCT)	⊕⊕⊕⊕ LOW 1 2	
	222 per 1000	38 per 1000 (2 to 684)				
Umbilical artery pH		The mean umbilical artery pH in the intervention group was 0.08 more (0.06 more to 0.1 more)	-	20 (1 RCT)	⊕⊕⊕⊕ MODERATE 2	
Abnormal FHR tracing	Study population		RR 0.57 (0.33 to 0.98)	20 (1 RCT)	⊕⊕⊕⊕ MODERATE 2	
	1000 per 1000	570 per 1000 (330 to 980)				
No improvement in FHR	Study population		RR 0.13 (0.03 to 0.59)	20 (1 RCT)	⊕⊕⊕⊕ MODERATE 2	Non-prespecified. See Differences between protocol and review
	1000 per 1000	130 per 1000 (30 to 590)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FHR:** fetal heart rate; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Confidence interval crossing the line of no effect (-1).

²Small sample size (-1).

³No events in either group (-1).

Summary of findings 8. Summary of findings for IV terbutaline versus IV nitroglycerin

IV terbutaline versus IV nitroglycerin for the management of intrapartum fetal distress

Patient or population: women with non-reassuring FHR tracing during labour or induction of labour

Setting: hospital in the USA with capacity for caesarean section

Intervention: IV terbutaline (250 µg)

Comparison: IV nitroglycerin (400 µg)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with IV nitroglycerin	Risk with IV terbutaline				
Perinatal death or severe morbidity	No data available					
Fetal or neonatal mortality	No data available					
Caesarean delivery	Study population		RR 0.96 (0.68 to 1.36)	110 (1 RCT)	⊕⊕⊕⊕ LOW ^{1 3}	
	547 per 1000	525 per 1000 (372 to 744)				
5-minute Apgar score < 7	Study population		not estimable	110 (1 RCT)	⊕⊕⊕⊕ LOW ^{2 3}	
	0 per 1000	0 per 1000 (0 to 0)				
Umbilical artery pH < 7.0	Study population		RR 4.87 (0.24 to 98.18)	75 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 3 4}	
	0 per 1000	0 per 1000 (0 to 0)				

Successful intrauterine fetal re-suscitation	Study population		RR 1.12	110	⊕⊕○○ LOW ^{1 3}	Non-prespecified. See Differences between protocol and review
	642 per 1000	718 per 1000 (559 to 932)	(0.87 to 1.45)	(1 RCT)		

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Confidence interval crossing the line of no effect (-1).

²No events in either group (-1).

³Small sample size (-1).

⁴Extremely wide confidence interval (-1).

BACKGROUND

Excessive uterine activity is termed uterine tachysystole or hyperstimulation, though the latter term should be abandoned because of potential confusion (ACOG 2009). Uterine tachysystole, defined as more than five uterine contractions per 10 minutes in at least two consecutive intervals (ACOG 2009), is not uncommon during labour (Crane 2001). It was documented in at least one-fifth of women with spontaneous onset of labour who had not received any labour augmentation, and in 48.6% of women whose labour had been induced by prostaglandin (Crane 2001). Similarly, non-reassuring fetal heart rate (FHR) patterns are commonly reported during active labour (Bloom 2006; Garite 2000). Although uterine tachysystole is more commonly noted after the use of labour-stimulating agents, it may also be a clinical sign of serious pregnancy complications, such as placental abruption or obstructed labour.

Description of the condition

Uterine contraction compresses maternal spiral arteries and increases the intraplacental pressure, profoundly reducing the placental blood flow when the intraplacental pressure exceeds the pressure of maternal perfusion to the placenta (Brar 1988; Fleischer 1987; McNamara 1995). It was reported that a contraction at 30 mmHg or more was able to diminish or even interrupt maternal blood flow to the placenta and potentially reduces fetal oxygenation status (Brar 1988; Fleischer 1987). In one study, fetal oxygenation saturation, quantitatively measured by an intrauterine sensor, reached its nadir 92 seconds after the peak of a contraction, and took another 90 seconds to obtain complete recovery (McNamara 1995). Normal labour with sufficient physiological relaxation time allows the oxygenation level of an uncompromised baby to be restored between contractions.

The compensatory fetoplacental mechanism may no longer be effective in the presence of uterine tachysystole, which is usually associated with strong contractions of 80 mmHg or more (Bakker 2007), and significantly shortened relaxation time. Strong contractions contribute to further compression of maternal spiral arteries, while a shortened relaxation time presumably does not allow the blood supply to the placenta to return to baseline levels before the next contraction (Peebles 1994). Uterine tachysystole was found to be associated with a progressive decrease of fetal oxygen saturation (FSpO₂) (Simpson 2008), and with a fall in fetal intracerebral oxygen saturation (Peebles 1994). In one study, five and six or more contractions per 10 minutes for 30 minutes resulted in 20% and 29% fetal oxygen desaturation, respectively (Simpson 2008). Importantly, tachysystole over a one-hour period in active labour can be correlated with a significantly increased risk of fetal acidosis. A study of 1433 women with singleton pregnancies in the Netherlands concluded that increased uterine activity in first and second stage is correlated with a higher incidence of umbilical artery pH of 7.11 or less (Bakker 2007). This can in turn lead to an increase in adverse neonatal sequelae (Hanskin 2003).

Description of the intervention

Intrauterine fetal resuscitation consists of interventions that aim to increase oxygen delivery to the placenta and enhance fetoplacental perfusion (ACOG 2009). National and international guidelines currently recommend intervention to correct non-reassuring FHR patterns or suspected fetal distress during labour (ACOG 2009),

FHR changes in the presence of excessive uterine activity (RCOG 2008), or excessive uterine activity in the absence of FHR changes (WHO 2011). The available interventions include discontinuation of any labour-stimulating agents, change of maternal position, administration of supplemental maternal oxygen, and if the abnormal FHR patterns persist, the use of tocolytic agents (ACOG 2009); the latter is the subject of this review. The use of tocolysis for assisting delivery at caesarean section is addressed by another Cochrane Review (Dodd 2006).

There is a wide range of tocolytic agents used acutely during labour for correcting uterine tachysystole, with or without the presence of suspected fetal distress. While studies have predominantly evaluated beta₂ (β₂)-adrenergic receptor agonists (Afschar 2004; Arias 1978; Briozzo 2007; Buhimschi 2002; De Heus 2008; Gerris 1980; Ingemarsson 1985; Magann 1993; Patriarco 1987; Pullen 2000; Sheybany 1982), some have also used magnesium sulphate (Magann 1993; Vigil-De Gracia 2000), nitric oxide donors (Buhimschi 2002; Pullen 2000), calcium channel blockers (Chao 2002), or oxytocin antagonists (Afschar 2004; De Heus 2008). Unfortunately, to date, no consistent recommendations on the indications for tocolytic therapy during labour, the preferred type of tocolytic agent, or the optimum dosage of these agents have been available.

How the intervention might work

Acute tocolysis inhibits uterine smooth muscle activity (Hubinont 2011), and has been used on the assumption that such relaxation improves placental perfusion and therefore may enhance fetal oxygenation (Simpson 2007). The intervention is employed to either improve fetal status and facilitate vaginal delivery, or as an interim method to improve fetal status whilst preparations for operative delivery are made (Kulier 1997; Simpson 2007). It is also possible that an improvement in the FHR trace may reduce caesarean section rates, given that a non-reassuring fetal heart tracing is one of the leading indications for emergency caesarean section (Barber 2011).

Why it is important to do this review

In an earlier Cochrane Review on tocolytics for suspected intrapartum fetal distress (Kulier 2000), betamimetic therapy was associated with a reduction of the number of FHR abnormalities. However the review did not assess whether tocolytics were effective in preventing or treating suspected fetal distress. This new review builds on the work of the Kulier 2000 study and will incorporate new evidence about the effects of different agents on uterine tachysystole which has emerged in recent years.

Regardless of advances in surgical and anaesthesia techniques, caesarean delivery is associated with a significantly increased risk of maternal mortality and morbidity (Lumbiganon 2010). Almost three-quarters of emergency caesarean deliveries were indicated for dystocia or suspected fetal distress (Stjernholm 2010; von Katterfeld 2011). Proper and timely management of excessive uterine activity during labour is expected to optimise the progress of labour, and reduce unnecessary caesarean deliveries. It is also expected to improve fetal condition, and therefore neonatal condition at birth.

The use of tocolytic therapy for uterine tachysystole (with or without accompanying suspected fetal distress) is however, not consistently recommended among clinical guidelines (ACOG

2009; RCOG 2008; WHO 2011). Acknowledging that only low-quality evidence is currently available, the World Health Organization (WHO) guideline on induction of labour made a weak recommendation of using betamimetic therapy for uterine hyperstimulation during induction of labour (WHO 2011). The inconsistency in clinical guidelines is presumably associated with inconsistent use of acute tocolysis in routine practice (Simpson 2005). Thus, an updated Cochrane Review will provide a synthesis of the latest evidence which can be used to guide clinical practice.

OBJECTIVES

To assess the effects of the use of acute tocolysis during labour for uterine tachysystole or suspected fetal distress, or both, on fetal, maternal and neonatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include all published randomised controlled trials (RCTs), including those using a cluster-RCT design. Due to the small number of identified studies, we decided to include abstracts if they met other eligibility criteria.

Studies using a cross-over or quasi-randomised design were not eligible in this review.

Types of participants

- Women with uterine tachysystole (defined as more than 5 contractions per 10 minutes in 2 consecutive intervals, or as defined by trial authors) without a non-reassuring fetal heart rate (FHR) pattern.
- Women with uterine tachysystole with a non-reassuring FHR pattern.
- Women with suspected fetal distress, diagnosed by FHR monitoring or fetal scalp pH measurement, and as defined by trial authors, with or without excessive uterine activity.

Types of interventions

- Tocolytics (such as beta₂ (β₂)-adrenergic receptor agonists, nitric oxide donors, calcium channel blockers, magnesium sulphate, oxytocin antagonists) versus placebo or no treatment.
- Comparison of different tocolytic agents.
- Tocolytics versus other treatments.

Types of outcome measures

Primary outcomes

1. Perinatal death or severe morbidity (at least one neonatal intensive care unit (NICU) admission for 24 hours or more, neonatal encephalopathy or convulsions).
2. Fetal or neonatal mortality.
3. Caesarean delivery.

Secondary outcomes

1. Abnormal FHR, as defined by trial authors.
2. Uterine tachysystole, with or without non-reassuring FHR patterns.

3. Postpartum haemorrhage (blood loss > 500 mL).
4. Requirement of additional tocolytic agent.
5. Maternal side effects (tachycardia, hypotension, dyspnoea, headache, nausea, syncope) and need to terminate treatment because of side effects.
6. Fetal oxygen saturation (FSpO₂), measured by an intrauterine FSpO₂ sensor.
7. Five-minute Apgar score less than seven.
8. Low umbilical artery pH (less than 7.0, or as defined by trial authors).
9. NICU admission.
10. Neonatal encephalopathy.
11. Neonatal convulsions.
12. Meconium-stained amniotic fluid.
13. Umbilical cord blood base excess/deficit.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (2 February 2018).

The Register is a database containing over 24,000 reports of controlled trials in the field of pregnancy and childbirth. For full current search methods used to populate Pregnancy and Childbirth's Trials Register, including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about [Cochrane Pregnancy and Childbirth](#) in the Cochrane Library and select the '**Specialized Register**' section from the options on the left side of the screen.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

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

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections ([Included studies](#); [Excluded studies](#)).

In addition, we searched [ClinicalTrials.gov](#) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), for unpublished, planned and ongoing trial reports (2 February 2018) using the search methods detailed in [Appendix 1](#).

Searching other resources

We searched the reference lists of retrieved studies. We did not apply any language or date restrictions.

Data collection and analysis

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors (SL and JV) independently assessed for inclusion all potential studies identified as a result of the search strategy. The abstracts of all studies identified from the search strategy were independently examined to ascertain the studies meeting the inclusion criteria. We obtained full study reports for those with uncertainty in eligibility. We resolved any disagreement through discussion or, if required, we consulted a third review author (JH).

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (SL and JV) independently extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, consulted a third review author (JH). We entered data into Review Manager software ([Review Manager 2014](#)), and checked for accuracy.

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

Assessment of risk of bias in included studies

Two review authors (SL and JV) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved any disagreement by discussion or by involving a third assessor (JH).

(1) Random sequence generation (checking for possible selection bias)

For each included study, we described 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 the intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment.

We then 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 assessed 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 assessed 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 included missing data in the analyses that 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.

The extent to which the outcome data were incomplete was assessed as:

- less than 5% incomplete outcome data;
- 5% to 9.9% incomplete outcome data;
- 10% to 19.9% incomplete outcome data;
- more than 20% incomplete outcome data.

(5) Selective reporting (checking for 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 prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified 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 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 for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered that it was likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses, however this was not possible for any of the included studies - see [Sensitivity analysis](#).

Assessing the quality of the body of evidence using the GRADE approach

We used the GRADE approach as outlined in the [GRADE handbook](#) in order to assess the quality of the body of evidence relating to the following outcomes for all comparisons.

1. Perinatal death or severe morbidity (at least one NICU admission for 24 hours or more, neonatal encephalopathy or convulsions).
2. Fetal or neonatal mortality.
3. Caesarean delivery.
4. Five-minute Apgar score less than seven.
5. Low umbilical artery pH (less than 7.0, or as defined by trial authors).
6. Abnormal FHR, as defined by trial authors.

We used [GRADEpro](#) Guideline Development Tool to import data from Review Manager 5 in order to create 'Summary of findings' tables (Review Manager 2014). We produced a summary of the intervention effect and a measure of quality for each of the above outcomes using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios (RRs) with 95% confidence intervals (CIs).

Continuous data

For continuous data, we used the mean difference (MD) if outcomes were measured in the same way between trials. We used the standardised mean difference (SMD) to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually-randomised trials, however we did not identify any. If, in future updates, we include cluster-randomised trials, we will adjust their sample sizes by the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using an estimate of the intracluster correlation coefficient (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.

A statistician will be involved in this part of the analysis.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, we will explore 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. 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 τ^2 , I^2 and χ^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 30% and either τ^2 was greater than zero, or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we planned to explore it by prespecified subgroup analysis, however we did not identify any.

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 5 software ([Review Manager 2014](#)). 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 we detected substantial statistical heterogeneity, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials. Where we used random-effects analyses, we presented the results as the average treatment effect with 95% CIs, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses, and consider whether an overall summary is meaningful. However, this was not necessary in this review.

We planned to carry out the following subgroup analysis.

1. The type of labour (induced labour or spontaneous labour).
2. The type of tocolytic agents given (β_2 -adrenergic receptor agonist, or magnesium sulphate, or nitric oxide donors, or oxytocin antagonist).
3. The indications for tocolysis (therapeutic tocolysis or preventive tocolysis. The latter is defined as tocolysis used for preventing fetal distress in the second stage of labour or at the same time as labour-stimulating agents are given).

We planned to explore the primary outcomes in subgroup analyses, however available data did not permit subgroup analyses in this review. We will perform planned subgroup analysis in future updates of this review, if appropriate.

Sensitivity analysis

We planned to carry out sensitivity analysis to explore the potential effect of study quality on the important outcomes, however the available data did not permit this. We will carry out planned sensitivity analyses in future updates of the review, if appropriate. Sensitivity analysis for trial quality will include high-quality studies rated as adequate for allocation concealment, to identify whether there are any substantive differences to the pooled result. If we include cluster-RCTs in our analyses along with the individually-randomised trials we will also carry out sensitivity analysis to investigate the effect of the randomisation unit. We will restrict all sensitivity analyses to the review's primary outcomes.

RESULTS

Description of studies

Results of the search

See: [Figure 1](#)

Figure 1. Study flow diagram.

The search retrieved 40 trial reports to assess. Of these 40 reports, 14 reports of eight studies met the inclusion criteria for the review (Afschar 2004; Briozzo 2007; Kulier 1997; Magann 1993; Pacheco 2006; Patriarco 1987; Pullen 2007; Rudra 2007). We excluded 26 reports of 20 studies (Buhimschi 2002; Burke 1989; Campbell

1978; Chao 2002; Cilliers 2013; Dunn 2016; Ekblad 1988; Gerris 1980; Goeschen 1985; Hidaka 1987; Humphrey 1975; Kashanian 2006a; Lipshitz 1976a; Lipshitz 1976b; Lipshitz 1976c; Lipshitz 1984; Sharami 2012; Taylor 1990; Torres 2001; Visser 1979),

Included studies

Eight studies (involving 734 women) met the inclusion criteria (Afschar 2004; Briozzo 2007; Kulier 1997; Magann 1993; Pacheco 2006; Patriarco 1987; Pullen 2007; Rudra 2007). The included studies explored a range of tocolytic interventions.

Design

All included studies were two-arm individually-randomised controlled trials, though none were placebo-controlled.

Sample sizes

Two studies described power calculations in determining their sample sizes (Briozzo 2007; Pullen 2007). The Briozzo 2007 study randomised 390 compared to the 392 required, whilst the Pullen 2007 study enrolled the 110 participants required. No other studies describe power calculations, and sample sizes were generally small, ranging from 26 to 75 participants.

Settings

All studies were undertaken in hospital settings, with the majority in high-income countries including the USA (Magann 1993; Pacheco 2006; Patriarco 1987; Pullen 2007), Austria (Afschar 2004), and Uruguay (Briozzo 2007). One was in South Africa (Kulier 1997), and one in Sri Lanka (Rudra 2007), upper and lower middle-income countries, respectively.

In all studies, participating facilities had the capacity to perform caesarean section.

Participants

Seven studies recruited women with signs of fetal distress on fetal heart rate (FHR) monitoring (Afschar 2004; Briozzo 2007; Kulier 1997; Magann 1993; Patriarco 1987; Pullen 2007; Rudra 2007), or on fetal scalp pH, or both (Patriarco 1987). The definition of fetal distress varied between trials (defined by the authors, as outlined in [Characteristics of included studies](#)). One of these studies (Briozzo 2007), excluded women with uterine tachysystole by including only women with a uterine contraction pattern of three to five in 10 minutes, whilst the others did not select women based on uterine activity. One study included women who were on an oxytocin infusion for augmentation of labour and who had uterine hyperstimulation, but who did not have signs of fetal distress on FHR monitoring (Pacheco 2006).

Four studies recruited women only when fetal distress had not resolved with "conservative" measures, which usually included maternal repositioning, intravenous (IV) fluids, oxygen, cessation of labour-augmenting agents and the option of amnioinfusion (Briozzo 2007; Magann 1993; Patriarco 1987; Pullen 2007). Four studies included women for whom the decision had already been made to deliver by caesarean section due to fetal distress (Kulier 1997; Magann 1993; Patriarco 1987; Rudra 2007).

In terms of gestational age, two studies included women at "term" (Briozzo 2007; Pacheco 2006), one included women at ≥ 38 weeks' gestation (Afschar 2004), one at > 35 weeks' gestation (Kulier 1997), and one at 32 to 42 weeks' gestation (Pullen 2007). Three did not specify a gestational age for inclusion (Magann 1993; Patriarco 1987; Rudra 2007), though the mean gestational ages for participants in the Magann 1993 and Patriarco 1987 studies fell between 38 and 40 weeks. All but one study required that included

women be in active labour, with the only exception being the Rudra 2007 study.

Only one study stated a cephalic presentation as an inclusion criterion (Briozzo 2007), and three included a singleton pregnancy as an inclusion criterion (Briozzo 2007; Pacheco 2006; Pullen 2007). Whilst not stated as inclusion criteria, the Afschar 2004 study only included women with a singleton pregnancy in a cephalic presentation at the time of randomisation.

Most studies excluded participants with severe maternal disease (e.g. pre-eclampsia, cardiac disease, metabolic diseases, hyperthyroidism, antepartum haemorrhage, chorioamnionitis), or fetal or placental abnormalities (e.g. intrauterine growth restriction, fetal malformations, placental abruption) (Afschar 2004; Briozzo 2007; Kulier 1997; Magann 1993; Pacheco 2006; Pullen 2007).

Interventions and comparisons

All eight studies examined a selective β_2 -adrenergic agonist, however the type of agonist varied between studies. Two studies compared administration of a selective β_2 -adrenergic agonist (IV hexoprenaline or subcutaneous terbutaline) to no tocolytic agent whilst awaiting emergency delivery (Kulier 1997; Patriarco 1987). Three studies evaluated subcutaneous terbutaline (a selective β_2 -adrenergic agonist), with one comparing it to IV magnesium sulphate (Magann 1993), one comparing it to no tocolytic agent, whilst awaiting emergency delivery (Patriarco 1987), and the third comparing two protocols: terbutaline with continuation of an oxytocin infusion compared to cessation of the oxytocin infusion without administration of a tocolytic agent (Pacheco 2006). A fourth study compared IV terbutaline to IV nitroglycerin (a nitric oxide donor) (Pullen 2007). One study compared IV atosiban (an oxytocin inhibitor) to IV hexoprenaline (a selective β_2 -adrenergic agonist) (Afschar 2004), one compared IV salbutamol (a selective β_2 -adrenergic agonist) to sublingual nifedipine (a calcium channel blocker) (Rudra 2007), and one compared IV fenoterol (a selective β_2 -adrenergic agonist) to emergency delivery (Briozzo 2007).

Outcomes

Primary outcomes for this review included perinatal death or severe morbidity, fetal or neonatal mortality, and caesarean section delivery. Only one study addressed the outcome of perinatal death or severe morbidity (Afschar 2004). Three studies reported on fetal or neonatal mortality (Afschar 2004; Kulier 1997; Patriarco 1987), though across all three studies there were only two perinatal deaths. Caesarean section rates were reported in four studies (Afschar 2004; Briozzo 2007; Pacheco 2006; Pullen 2007). Several studies did not report on caesarean section rates, as the decision was made prior to randomisation to deliver all participants by caesarean section.

Secondary outcomes for the review included neonatal, maternal and labour outcomes.

The Rudra 2007 study did not present data for any primary or secondary outcomes in a format that could be analysed for this review. All other studies addressed umbilical artery pH, although cut-offs used varied from 7.00 to 7.20, and all except the Magann 1993 study reported on five-minute Apgar scores less than seven. Two studies reported umbilical artery base excess

(Briozzo 2007; Kulier 1997), whilst none reported on intrauterine fetal oxygen saturation (FSPO₂). Three studies reported on rates of admission to neonatal intensive care units (NICUs) (Afschar 2004; Briozzo 2007; Kulier 1997). Five studies reported if there was an abnormal FHR tracing following treatment, with the individual study outcomes including whether the FHR pattern improved or remained unchanged (Kulier 1997; Magann 1993), or whether there was a complete resolution of the non-reassuring FHR pattern within 10 minutes and whether such a pattern recurred (Pullen 2007). Two studies did not prespecify this outcome but reported it: the Afschar 2004 study reported on the number of participants with "recovery to normal fetal heart rate", and the Patriarco 1987 study reported on whether FHR decelerations were detected after treatment, and whether they had changed in their amplitude and frequency. We considered this spectrum of reporting on FHR abnormalities by the review authors to satisfy the prespecified outcome of "abnormal FHR, as defined by study authors". Two studies reported on the presence of meconium-stained liquor (Kulier 1997; Pullen 2007). Two studies reported on rates of uterine tachysystole following treatment, defined by the Pullen 2007 study as resolution of tachysystole within 10 minutes and by the Magann 1993 study as the mean difference (MD) in Montevideo units in the 10 minutes before and the 10 minutes following treatment. One study reported on rates of postpartum haemorrhage (Pullen 2007), though the Magann 1993 study did report the mean estimated blood loss for participants. Two studies reported on maternal side effects. This was defined by the Afschar 2004 study as palpitations or tachycardia, whilst the Patriarco 1987 study reported only whether "side effects" were noticed. Only one study reported on whether a subsequent tocolytic was required (Pullen 2007). No studies reported rates of neonatal encephalopathy or neonatal convulsions.

Sources of funding

Atosiban was supplied by Ferring Pharmaceuticals for the Afschar 2004 study, however sources of funding for the other studies was otherwise not disclosed (Briozzo 2007; Kulier 1997; Magann 1993; Pacheco 2006; Patriarco 1987; Pullen 2007; Rudra 2007).

Declarations of interest

The authors of the Afschar 2004 study reported no personal financial support; there was no comment on other potential conflicts of interest. No other trials included declarations on conflicts of interest (Briozzo 2007; Kulier 1997; Magann 1993; Pacheco 2006; Patriarco 1987; Pullen 2007; Rudra 2007).

Excluded studies

After assessment of study eligibility, we excluded 20 studies. The main reasons for exclusion was that the study did not include participants with uterine tachysystole or suspected fetal distress (13 studies: Buhimschi 2002; Campbell 1978; Chao 2002; Cilliers 2013; Dunn 2016; Ekblad 1988; Gerris 1980; Humphrey 1975; Lipshitz 1976a; Lipshitz 1976b; Lipshitz 1976c; Taylor 1990; Torres 2001), or no tocolytic intervention was used (three studies: Goeschen 1985; Kashanian 2006a; Sharami 2012). Four studies were not RCTs (Burke 1989; Hidaka 1987; Lipshitz 1984; Visser 1979).

Ongoing studies

We did not identify any ongoing studies.

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Afschar 2004	?	+	?	?	+	+	+
Briozzo 2007	+	+	-	?	+	-	-
Kulier 1997	+	+	?	?	-	+	?
Magann 1993	+	+	-	+	+	+	+
Pacheco 2006	+	+	-	-	+	?	+
Patriarco 1987	+	?	-	?	+	+	+
Pullen 2007	+	+	+	+	+	+	+
Rudra 2007	?	?	?	?	?	?	?

Allocation

Random sequence generation (selection bias)

Of the eight included trials, we assessed six as having adequate randomisation methods. Three studies used computer-generated

randomisation in blocks of 10 (Kulier 1997), blocks of 20 (Briozzo 2007), or by simple randomisation (Pacheco 2006). Two studies used a random number table (Magann 1993; Pullen 2007). One study used "randomly generated numbers" (Patriarco 1987). The method of randomisation was unclear in two studies: one

described randomisation as being performed by "treatment boxes" without an explanation of what these were (Afschar 2004), whilst the other did not describe the randomisation process (Rudra 2007).

Allocation concealment (selection bias)

We rated two of the included studies as unclear for allocation concealment (Patriarco 1987; Rudra 2007). We judged the remainder to have a low risk of bias. Two studies used sealed opaque envelopes (Kulier 1997; Magann 1993), whilst two used sealed envelopes that were not specified to be opaque (Briozzo 2007; Pacheco 2006). One had the allocation stored offsite (Afschar 2004), and one used a concealed chart that was only available to the labour and delivery nurse preparing the study medication (Pullen 2007).

Blinding

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

Blinding of participants was unclear or not discussed in three studies (Afschar 2004; Kulier 1997; Rudra 2007). There was a high risk of bias in four studies, in which blinding was not discussed and the interventions were dissimilar enough that the allocation was likely known to participants and personnel (Briozzo 2007; Magann 1993; Pacheco 2006; Patriarco 1987). There was a low risk of bias in one study in which women and personnel (except for the nurse preparing the medication) were blinded to the treatment group and the interventions appeared similar (Pullen 2007).

Blinding of outcome assessment (checking for possible detection bias)

Blinding of outcome assessors was unclear or not described in four reports (Afschar 2004; Kulier 1997; Patriarco 1987; Rudra 2007). We also judged the Briozzo 2007 study to have an unclear risk of bias, as the authors described blinding of neonatologists (who assessed the Apgar score) but did not discuss who assessed the other neonatal outcomes or whether there was any blinding for maternal outcome assessment. We judged one study to have a high risk of bias in outcome assessment as the authors did not discuss blinding (Pacheco 2006), and all participants were observed until delivery by the primary investigator. We assessed two studies to be at low risk of detection bias (Magann 1993; Pullen 2007).

Incomplete outcome data

We were unable to assess attrition in one study (Rudra 2007). The risk of incomplete outcome data was high in the Kulier 1997 study, which had incomplete data for some outcomes but did not provide any justification for this. We judged the remaining studies to have a low risk of attrition bias with low rates of attrition and no differences between groups in terms of characteristics and numbers lost to follow-up (Afschar 2004; Briozzo 2007; Magann 1993; Pacheco 2006; Patriarco 1987; Pullen 2007).

Selective reporting

We judged the risk of reporting bias to be high for one study due to a combination of factors (Briozzo 2007): we could not locate the study protocol, making it difficult to assess how outcomes were defined before and after the trial; there were also some outcomes that were reported as significant in the text without supporting data, as well as a non-prespecified "special" subgroup analysis. We judged the risk of reporting bias as unclear in the Rudra 2007 and Pacheco 2006

studies as outcomes were not clearly prespecified, and judged all other included studies as low risk of bias (Afschar 2004; Kulier 1997; Magann 1993; Patriarco 1987; Pullen 2007), with reported outcomes being consistent with prespecified definitions.

Other potential sources of bias

The sample sizes in the included trials were generally very small, which may have reduced the sensitivity of the studies to detect rarer outcomes.

We judged the Briozzo 2007 study to be at high risk of other bias as it effectively introduced an additional inclusion criteria in the study design by including only those women who had electronic FHR monitoring. In their study, this was only used in women who were at a higher risk and had at least one of: previous perinatal demise; maternal age greater than 40; pathologies during pregnancy; alterations in fetal growth and development; dystocic labour; gestational age greater than 41 weeks; prelabour rupture of membranes; or antepartum haemorrhage in the third trimester.

Kulier 1997 did not clearly define the management of the comparison group in their paper, however we presumed that the comparison group did not receive medication whilst awaiting delivery. In addition, the study did not prespecify cut-off values for their study outcomes, however, the values used were clinically reasonable - as assessed this study as having an 'unclear' risk of bias. There was limited information in the trial report by Rudra 2007 and we assessed this study as having an 'unclear' risk of other bias.

We assessed Afschar 2004; Magann 1993; Patriarco 1987; Pacheco 2006 and Pullen 2007 as having a 'low' risk of other bias.

Magann 1993 and Patriarco 1987 studies did not prespecify cut-off values for their study outcomes, however those used were clinically reasonable. Only one study specified authors' conflicts of interests and sources of funding (Afschar 2004), with atosiban being provided by Ferring pharmaceuticals. The Magann 1993 study was supported in part by the Vicksburg Hospital Medical Foundation. No other studies reported on their sources of funding or support or any potential conflicts of interest.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings for selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery; **Summary of findings 2** Summary of findings for IV atosiban versus IV hexoprenaline; **Summary of findings 3** Summary of findings for IV fenoterol bromhydrate versus emergency delivery; **Summary of findings 4** Summary of findings for IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery; **Summary of findings 5** Summary of findings for subcutaneous terbutaline versus IV magnesium sulphate; **Summary of findings 6** Summary of findings for subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic agent; **Summary of findings 7** Summary of findings for subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery; **Summary of findings 8** Summary of findings for IV terbutaline versus IV nitroglycerin

We included nine reports of eight studies (involving 734 women) in this review, however all but one of the comparisons (comparison 1) are based on data from single studies, most with small sample sizes.

The GRADE outcomes included in this review were:

1. perinatal death or severe morbidity (at least one NICU admission for 24 hours or more, neonatal encephalopathy or convulsions);
2. fetal or neonatal mortality;
3. caesarean delivery;
4. five-minute Apgar score less than seven;
5. low umbilical artery pH (less than 7.0 or as defined by trial authors);
6. abnormal FHR, as defined by trial authors.

Where the results for a given outcome are not reported for individual comparisons, the included trial(s) did not report on that outcome.

Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery

Two studies (involving 57 women) compared a selective β_2 -adrenergic agonist to no tocolytic agent after the decision to proceed to urgent caesarean section had been made. The [Kulier 1997](#) study included women in active labour, at or beyond a gestational age of 35 weeks, for whom the decision had been made to deliver by caesarean section for fetal distress. Women were randomised to receiving 10 μ g of IV hexoprenaline or no tocolytic medication whilst awaiting delivery. The [Patriarco 1987](#) study included women in labour with signs of fetal distress that had not responded to conservative measures and with a fetal scalp pH less than 7.25. Women were randomised to receiving 250 μ g of subcutaneous terbutaline or no tocolytic medication whilst preparations for urgent caesarean section were being made.

Primary outcomes

Perinatal death or severe morbidity

Neither of the studies reported on this outcome.

Fetal or neonatal mortality

There were no perinatal deaths in the study by [Patriarco 1987](#). Two stillbirths were reported in the [Kulier 1997](#) study, both of which occurred in the control group. One was discovered to have gross hydrocephalus at the time of delivery, and the second had been referred with fetal distress from a peripheral clinic and was delivered vaginally after 55 minutes whilst awaiting caesarean delivery (risk ratio (RR) 0.23, 95% confidence interval (CI) 0.01 to 4.55; 2 studies, 57 women; [Analysis 1.1](#)). We determined the GRADE quality of evidence to be low, as we downgraded two levels for imprecision ([Summary of findings for the main comparison](#)).

Caesarean delivery

The decision to deliver by caesarean section had been made for all women in these studies prior to inclusion and randomisation, and so we were unable to address this outcome in this analysis.

Secondary outcomes

We are uncertain about the effect of the intervention on the rate of **five-minute Apgar scores less than seven** (RR 0.20, 95% CI 0.02 to 1.57; 2 studies, 55 women; low-quality evidence; [Analysis 1.2](#)). There were no cases of five-minute Apgar scores less than seven in the tocolysis group compared to two cases in the group that did not receive tocolysis. There were no data available regarding **umbilical**

artery pH. There were probably fewer babies in the treatment group that had **no improvement in FHR tracing** compared to the control group (average RR 0.28, 95% CI 0.08 to 0.95; $\text{Tau}^2 = 0.48$, $I^2 = 57\%$, 2 studies, 43 women; moderate-quality evidence; [Analysis 1.3](#)) (non-prespecified outcome).

IV atosiban versus IV hexoprenaline

One study involving 26 women, compared atosiban, an oxytocin antagonist, to hexoprenaline, a selective β_2 -adrenergic agonist ([Afschar 2004](#)), for the management of fetal distress. Women in labour beyond 38 weeks' gestation with a severe fetal bradycardia (< 80 bpm for more than 3 minutes) were randomised to receive either 6.75 mg of IV atosiban or 5 μ g of IV hexoprenaline.

Primary outcomes

Perinatal death or severe morbidity

One infant in the IV hexoprenaline group was admitted to the NICU for > 24 hours following delivery by forceps, and was discharged well five days later (RR 0.33, 95% CI 0.01 to 7.50; low-quality evidence; [Analysis 2.1](#)).

Fetal or neonatal mortality

There were no perinatal deaths in either group ([Analysis 2.2](#)). The effect was not estimable, and the quality of evidence was low.

Caesarean delivery

One infant in the IV hexoprenaline group was delivered by caesarean section, and none in the IV atosiban group (RR 0.33, 95% CI 0.01 to 7.50; low-quality evidence; [Analysis 2.3](#)).

Secondary outcomes

No infants in either group had **five-minute Apgar scores less than seven** ([Analysis 2.4](#)). The effect was not estimable, and the quality of evidence was very low; it is uncertain whether the intervention has an effect on this outcome.

There were no differences detected between women treated with atosiban compared to those treated with hexoprenaline in terms of the **mean umbilical artery pH** (mean difference (MD) 0.00 pH, 95% CI -0.05 to 0.05; low-quality evidence; [Analysis 2.5](#)), the rate of **abnormal FHR tracings** (RR 3.00, 95% CI 0.13 to 67.51; low-quality evidence; [Analysis 2.6](#)), or the number of **admissions to the NICU** (RR 0.33, 95% CI 0.01 to 7.50; [Analysis 2.8](#)). Only one case in the atosiban group had an abnormal FHR tracing compared to none in the hexoprenaline group, whilst one infant in the hexoprenaline group was admitted to the NICU compared to none in the atosiban group. Women who received atosiban were less likely to experience **maternal side effects** (tachycardia or palpitations) than those who received hexoprenaline (RR 0.10, 95% CI 0.01 to 0.67; [Analysis 2.7](#)).

IV fenoterol bromhydrate versus emergency delivery

The [Briozzo 2007](#) study, involving 390 women, compared fenoterol, a selective β_2 -adrenergic agonist, to emergency delivery as soon as possible for the management of fetal distress. Women in labour at term who had a fetus in a cephalic presentation and who did not have uterine tachysystole were eligible for inclusion in the event of a non-reassuring FHR tracing without an identified reversible cause. Women were randomised to receive intrauterine fetal resuscitation with an IV infusion of fenoterol (0.1 mg/minute,

titrated according to response) or emergency delivery (either caesarean section or instrumental vaginal delivery, depending on the clinical scenario). Those in the fenoterol group were reassessed after 10 minutes based on uterine contractility and FHR tracings: if the fetal situation remained unchanged or had worsened, the intervention was considered ineffective and emergency delivery was performed as soon as possible; if the fetal situation had improved, the intervention was considered effective and the FHR tracing and uterine activity was monitored for a further 20 minutes before performing emergency delivery.

Primary outcomes

Perinatal death or severe morbidity

There were no data reported for perinatal death or severe morbidity.

Fetal or neonatal mortality

There were no data reported for fetal or neonatal mortality.

Caesarean delivery

Fenoterol probably increases the risk of caesarean delivery compared to emergency delivery (RR 1.12, 95% CI 1.04 to 1.22; moderate-quality evidence; [Analysis 3.1](#)). Of those in the emergency delivery group who were not delivered by caesarean section, 19 (9.6%) were delivered by spontaneous vaginal birth and 19 (9.6%) by forceps. In the fenoterol group, nine (4.7%) were delivered by spontaneous vaginal birth and nine (4.7%) by forceps. The authors attributed this to the fact that fenoterol diminished uterine contractility due to its tocolytic effect, which was proposed to reduce the likelihood of vaginal delivery.

Secondary outcomes

Fenoterol may have little or no effect on the risk of **five-minute Apgar scores less than seven** (RR 1.28, 95% CI 0.35 to 4.68; low-quality evidence; [Analysis 3.2](#)), or on the rate of **umbilical artery pH less than 7.1** (RR 0.68, 95% CI 0.44 to 1.05; low-quality evidence; [Analysis 3.3](#)), or **umbilical artery base excess < -12** (RR 0.67, 95% CI 0.46 to 1.00; [Analysis 3.4](#)). No data were available regarding **abnormal FHR**. Infants of women in the fenoterol group were less likely to need **admission to the NICU** than those who were randomised to emergency delivery (RR 0.47, 95% CI 0.27 to 0.81; [Analysis 3.5](#)).

IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery

The [Kulier 1997](#) study, involving 37 women, compared IV hexoprenaline, a selective β_2 -adrenergic agonist, to no tocolytic agent in women awaiting emergency delivery for the management of fetal distress. The study included women beyond 35 weeks' gestation who were in active labour, and for whom a decision had been made to deliver by caesarean section due to fetal distress based on FHR tracing. Once randomised, women received either hexoprenaline or no tocolytic whilst awaiting caesarean section - the randomisation-to-delivery interval was not significantly different between the groups.

Primary outcomes

Perinatal death or severe morbidity

There were no data reported for perinatal death or severe morbidity.

Fetal or neonatal mortality

There were two fetal deaths in the group that did not receive any tocolytic agent (RR 0.23, 95% CI 0.01 to 4.55; low-quality evidence; [Analysis 4.1](#)) - one of these was found to have gross hydrocephalus at the time of delivery, and the other was stillborn by vaginal delivery after 55 minutes whilst awaiting caesarean section after being transferred from a peripheral facility with fetal distress. There were no neonatal deaths in either group.

Caesarean delivery

The rate of caesarean delivery was not reported in this study, however women were only randomised once the decision had already been made to deliver by caesarean section. There was one vaginal delivery reported in the group that did not receive a tocolytic agent, which was the stillborn that delivered whilst awaiting caesarean section.

Secondary outcomes

There were two babies with Apgar scores below seven at five minutes (RR 0.24, 95% CI 0.01 to 4.57; low-quality evidence; [Analysis 4.2](#)), with both occurring in the group that received no tocolytic.

There was little or no difference in the incidence of **umbilical artery pH less than 7.2** (RR 0.64, 95% CI 0.30 to 1.35; low-quality evidence; [Analysis 4.3](#)). There was probably a reduced likelihood of there being **no improvement in the FHR tracing** (non-prespecified outcome) in the IV hexoprenaline group (RR 0.43, 95% CI 0.21 to 0.88; moderate-quality evidence; [Analysis 4.4](#)). There was no clear difference in the incidence of **umbilical artery base excess < -10** (RR 0.43, 95% CI 0.13 to 1.37; [Analysis 4.6](#)). There was just one **admissions to the NICU**, in the IV hexoprenaline group (RR 3.50, 95% CI 0.15 to 80.71; [Analysis 4.7](#)). The incidence of **meconium-stained amniotic fluid** was less likely in the hexoprenaline group (3/17) compared to the no tocolytic control (12/19) (RR 0.28, 95% CI 0.09 to 0.83; [Analysis 4.5](#)).

Subcutaneous terbutaline versus IV magnesium sulphate

Two reports of one study involving 46 women, compared subcutaneous terbutaline, a selective β_2 -adrenergic agonist, to IV magnesium sulphate for the management of fetal distress ([Magann 1993](#)). The study included women who were in active labour with signs of fetal distress which had not responded to conventional approaches (oxytocic discontinuation, fluid bolus, positional change, oxygen or amnioinfusion), and for whom the decision had been made to deliver by caesarean section. Eligible women were randomised to receive 250 μ g of subcutaneous terbutaline or a 4 g bolus of IV magnesium sulphate, with caesarean section commenced within 15 minutes of receiving the study drug.

Primary outcomes

Perinatal death or severe morbidity

There were no data available to analyse perinatal death or severe morbidity.

Fetal or neonatal mortality

There were no data available to analyse fetal or neonatal mortality.

Caesarean delivery

All women in this study were delivered by caesarean section; participants were only randomised once the decision had been made for delivery by caesarean section, and this was performed within 15 minutes of the tocolytic drug in all cases. Therefore it was not possible to assess the impact of the intervention on caesarean section rate.

Secondary outcomes

There were no data available regarding **five-minute Apgar scores**. We are uncertain about the effects of terbutaline or magnesium sulphate on the risk of umbilical artery pH less than 7.2 (RR 0.29, 95% CI 0.07 to 1.23; very low-quality evidence; [Analysis 5.1](#)), or the likelihood of **resolution of fetal distress** (non-prespecified outcome) (RR 1.31, 95% CI 0.97 to 1.77; very low-quality evidence; [Analysis 5.2](#)). Given the quality of the evidence, it is uncertain whether the intervention reduces or increases the likelihood of these outcomes. The [Magann 1993](#) study also reported there to be no difference between groups in terms of estimated volume of **blood loss** (mL) (MD -53.00, 95% CI -233.33 to 127.33 (data not in our analyses).

Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic agent

The [Pacheco 2006](#) study, involving 28 women, compared two protocols for the management of uterine hyperstimulation in women receiving an oxytocin infusion: subcutaneous terbutaline (a selective β_2 -adrenergic agonist) with continuation of the oxytocin infusion versus cessation of the oxytocin infusion without a tocolytic agent. Women who were in active labour at term were included if they were receiving an oxytocin infusion for augmentation of labour and developed uterine hyperstimulation which did not resolve spontaneously within 20 minutes. Women were randomised to either receive 250 μ g of subcutaneous terbutaline (up to 3 doses 15 minutes apart if hyperstimulation did not resolve) whilst the oxytocin infusion was continued, or to have the oxytocin infusion ceased without receiving any tocolytics. If uterine hyperstimulation persisted after three doses of terbutaline in the treatment group, then the oxytocin infusion was ceased. Participants with a non-reassuring FHR tracing (i.e. fetal distress) were excluded from this study.

Primary outcomes

Perinatal death or severe morbidity

There were no data available to analyse perinatal death or severe morbidity.

Fetal or neonatal mortality

There were no data available to analyse fetal or neonatal mortality.

Caesarean delivery

There may be little or no difference between the subcutaneous terbutaline group (8/15) and the control (4/13) in terms of the rate of caesarean delivery (RR 1.73, 95% CI 0.68 to 4.45; low-quality evidence; [Analysis 6.1](#)).

Secondary outcomes

There were no babies with **five-minute Apgar scores less than seven** ([Analysis 6.2](#)), or **umbilical artery pH less than 7.0** ([Analysis 6.3](#)), making the relative effect inestimable. The GRADE quality of evidence was very low for both outcomes. There were no data available regarding **abnormal FHR**. The time taken for uterine hyperstimulation to resolve following treatment appeared to be shorter in the terbutaline group compared to the group for whom oxytocin was ceased (MD -25.19 minutes, 95% CI -39.96 to -10.42; [Analysis 6.4](#)), whilst there was no difference detected in the rate of recurrence of uterine hyperstimulation after the initial episode had resolved (RR 0.52, 95% CI 0.15 to 1.77; [Analysis 6.5](#)) (both non-prespecified outcomes).

Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery

The [Patriarco 1987](#) study, involving 20 women, compared subcutaneous terbutaline, a selective β_2 -adrenergic agonist, to no tocolytic agent in women awaiting emergency delivery for the management of fetal distress. The study included women who were in labour with signs of fetal distress that had not responded to conservative management, and who had a fetal scalp blood sample with a pH less than 7.25. Eligible participants were randomised to receive either 250 μ g of subcutaneous terbutaline or no tocolytic medication whilst preparations were being made for urgent caesarean section.

Primary outcomes

Perinatal death or severe morbidity

The study authors stated that there were no differences in neonatal morbidity between the two groups, however morbidity was not defined and there was no mention of how many, if any, fetuses or neonates were defined as having morbidity.

Fetal or neonatal mortality

There were no perinatal deaths in either group ([Analysis 7.1](#)). The relative effect was therefore not estimable, and the quality of evidence was low.

Caesarean delivery

All women in this study were delivered by caesarean section; participants were only randomised once the decision had been made for delivery by caesarean section.

Secondary outcomes

There was no little or no difference detected between those who received terbutaline and those who did not in the rate of **five-minute Apgar scores less than seven** (RR 0.17, 95% CI 0.01 to 3.08; low-quality evidence; [Analysis 7.2](#)), however the certainty in this result was low with two events in the control group compared to none in the intervention group. The mean **umbilical artery pH** was probably slightly higher in the group that received terbutaline (MD 0.08 pH, 95% CI 0.06 to 0.10; moderate-quality evidence; [Analysis 7.3](#)).

Those who received terbutaline were probably less likely to have an **abnormal FHR** following treatment (6/11) than the 'no tocolytic' control group (9/9) (RR 0.57, 95% CI 0.33 to 0.98; moderate-quality evidence; [Analysis 7.4](#)), or to be classified as having **no**

improvement in FHR (non-prespecified outcome) (RR 0.13, 95% CI 0.03 to 0.59; [Analysis 7.5](#)).

No **maternal side effects** were reported in the treatment group, however the rate was not reported for the control group. Therefore, we cannot draw any conclusions regarding this outcome.

IV terbutaline versus IV nitroglycerin

The [Pullen 2007](#) study, involving 110 women, compared IV terbutaline, a selective β_2 -adrenergic agonist, to IV nitroglycerin (a nitric oxide donor) for the management of fetal distress. Women who were in labour or who were admitted for induction of labour, and who were between 32 and 42 weeks' gestational age, were included if they had a non-reassuring FHR tracing that did not respond to conservative management. Eligible women were randomised to receive either 250 μ g of IV terbutaline or 400 μ g of IV nitroglycerin.

Primary outcomes

Perinatal death or severe morbidity

There were no data available to analyse perinatal death or severe morbidity.

Fetal or neonatal mortality

There were no data available to analyse fetal or neonatal mortality.

Caesarean delivery

There may be little or no difference between the terbutaline group (30/57) and the nitroglycerin group (29/53) in the rate of caesarean section (RR 0.96, 95% CI 0.68 to 1.36; low-quality evidence; [Analysis 8.1](#)).

Secondary outcomes

No women in either group had **five-minute Apgar scores less than seven** ([Analysis 8.2](#)), making the relative effect inestimable (low-quality evidence.) We are uncertain of the effects on **umbilical artery pH less than 7.0** (RR 4.87, 95% CI 0.24 to 98.18; very low-quality evidence; [Analysis 8.3](#)), however numbers were low with two events in the terbutaline group and none in the nitroglycerin group. There appeared to be no clear difference in the rate of **successful intrauterine fetal resuscitation** (non-prespecified outcome) (RR 1.12, 95% CI 0.87 to 1.45; [Analysis 8.6](#)).

Those in the terbutaline group (1/57) were less likely to have **uterine tachysystole** 10 minutes after drug administration compared to the nitroglycerin group (10/53) (RR 0.09, 95% CI 0.01 to 0.70; [Analysis 8.4](#)), however there was no clear difference in the need for a **repeat dose of tocolytic agent** (RR 1.24, 95% CI 0.57 to 2.70; [Analysis 8.5](#)). There was also no difference detected between the terbutaline and the nitroglycerin group in terms of the presence of **meconium-stained amniotic fluid** (RR 0.93, 95% CI 0.51 to 1.71; [Analysis 8.7](#)), **admission to the NICU** (RR 0.93, 95% CI 0.46 to 1.89; [Analysis 8.8](#)), or **postpartum haemorrhage** (RR 1.39, 95% CI 0.24 to 8.02; [Analysis 8.9](#)).

IV salbutamol versus sublingual nifedipine

The [Rudra 2007](#) study, involving 75 women, compared IV salbutamol, a selective β_2 -adrenergic agonist, to sublingual nifedipine, a calcium channel blocker, for the management of fetal distress. This study was presented in abstract form with

limited description of the methods used. Women with severe cardiotocographic abnormalities were included once the decision had been made to perform an urgent caesarean section. The dosage and administration protocol of the two treatments was not described.

Primary outcomes

Perinatal death or severe morbidity

There were no data available to analyse perinatal death or severe morbidity.

Fetal or neonatal mortality

There were no data available to analyse fetal or neonatal mortality.

Caesarean delivery

There were no data available to analyse caesarean section rates. Women were only included once the decision had already been made to deliver by urgent caesarean section.

Secondary outcomes

There were no data that were presented in a form that was able to be entered into the data analysis for this review. The study authors did note that women treated with salbutamol had a higher rate of maternal side effects, uterine hypotonia and peripartum blood loss than those treated with nifedipine. Whilst they report that there was no significant influence on perinatal outcomes, infants in the nifedipine group were significantly more likely to require ventilatory support after delivery (30.5% versus 7.7%).

DISCUSSION

Summary of main results

This review included eight studies (involving 734 women), however, all but one of our comparisons were based on data from single studies with small numbers of participants. All of the included studies used a selective β_2 -agonist in one of their study arms, however, the specific drug varied from study to study, as did the comparison. Overall, the use of a tocolytic agent appeared to improve some measures of fetal well-being and reduce uterine tachysystole, though no studies demonstrated any improvement in neonatal condition, or in the primary outcomes for the review. However, the limited data for most outcomes means specific conclusions cannot be drawn.

Regarding specific comparisons:

1. Women who received a selective β_2 -adrenergic agonist whilst awaiting emergency delivery for fetal distress were more likely to experience an improvement in the fetal heart rate (FHR) tracing than those who received no treatment. There was no difference detected between the groups in the rate of Apgar scores less than seven at five minutes, and the intervention may make little or no difference to this outcome.
2. Atosiban for the treatment of fetal distress was associated with fewer cases of maternal palpitations or tachycardia than hexoprenaline, with no differences detected between the two across other outcomes. The small sample size means that rare events, such as fetal or neonatal mortality or severe morbidity, were unlikely to be detected.

3. Women who received fenoterol for fetal distress were less likely to have infants that required admission to a neonatal intensive care unit (NICU) than women who were delivered by emergency delivery, however they were more likely to deliver by caesarean section. This was hypothesised to be due to reduced uterine contractility in the fenoterol group, reducing the likelihood of a vaginal delivery. We did not detect any differences across any other outcomes.
4. Women who received hexoprenaline whilst awaiting emergency delivery for fetal distress, compared to those who did not, were less likely to have meconium-stained liquor and were more likely to show an improvement in the FHR tracing. We did not detect any differences between groups in other outcomes, including mortality and morbidity, Apgar scores, umbilical artery pH or NICU admission.
5. Women who received terbutaline whilst awaiting emergency delivery, compared to those who did not, were more likely to show an improvement in the FHR tracing. We did not detect any differences in any other outcomes including Apgar score, umbilical artery pH or maternal side effects.
6. We did not detect any differences in the umbilical artery pH, resolution of fetal distress or maternal blood loss between women treated with terbutaline for fetal distress and those treated with magnesium sulphate.
7. Women treated with terbutaline for fetal distress were less likely to have uterine tachysystole following treatment than those treated with nitroglycerin, however we did not detect any differences between groups in caesarean section rates, successful intrauterine fetal resuscitation or measures of neonatal well-being postpartum.
8. In women receiving oxytocin for labour augmentation who developed uterine hyperstimulation, hyperstimulation resolved faster in women who received terbutaline and continued the oxytocin compared to those who had the oxytocin infusion ceased. We did not detect any differences between the groups in terms of caesarean section rates, Apgar scores or umbilical artery pH. The rate of recurrence of uterine hyperstimulation was also not different between groups.

Overall completeness and applicability of evidence

We were unable to pool findings for most interventions due to the heterogeneity in intervention and comparison groups and reported outcomes. Many of the outcomes that are of key clinical significance in this context, such as maternal morbidity and fetal and neonatal mortality and morbidity, are rare events (particularly in higher-income countries), and the small sample sizes mean that the sensitivity of the included studies for detecting these events was very low.

It was difficult to directly compare studies due to the variety of interventions and outcome definitions used, meaning only one meta-analysis was possible. In the only two studies that we could meta-analyse, the study protocols and drug used (β_2 -adrenergic agonist) differed, hence the clinical applicability of the findings are unclear.

The majority of studies are from high-income countries in facilities with access to caesarean section, which may limit the generalisability of the results to lower-resource settings, or settings where caesarean section is not available.

Quality of the evidence

The methodological qualities of the studies included was variable. One was published only in abstract form and did not include enough information to assess any aspects of bias. Most studies used adequate randomisation and allocation concealment. No studies were placebo-controlled, and blinding was inadequate or impossible in all but one study due to the significant differences between interventions in terms of approach to management or route of drug administration. Overall, the included studies had a low risk of bias for random sequence generation, allocation concealment, incomplete data and selective reporting, and a high risk of bias in blinding methods.

There was generally not a clearly defined management pathway for women in control groups, in terms of medications they could and could not receive in the trial - this could introduce potential confounders that were not assessed. There was limited blinding of outcome assessment, with only two studies adequately blinding assessors. We judged most studies to have a low risk of both reporting and attrition bias.

We assessed the quality of the evidence using the GRADE system, and generally found it to be of low- to moderate-quality. We downgraded all studies by one or two levels for imprecision, and also some due to risk of bias.

Potential biases in the review process

There is potential for bias in each step of the review process, however we attempted to limit this. Our search strategy was supported by Cochrane Pregnancy and Childbirth, and at least two review authors evaluated each identified study for inclusion, data extraction and quality assessment. In cases of disagreement, results were discussed and a third review author was consulted. One review author (JH) was a co-author of an included study (Kulier 1997), and was not involved in any decisions or assessments pertaining to this study. Despite our efforts, any assessment of studies is subjective in nature; a different team of review authors may have made a different assessment of the evidence.

Agreements and disagreements with other studies or reviews

The previous Cochrane Review on tocolytics for suspected intrapartum fetal distress (Kulier 2000), found that betamimetics reduced FHR abnormalities and uterine activity, however, it found insufficient evidence to comment on clinically important outcomes or evaluate the role of betamimetics for suspected fetal distress. Our review includes six additional studies compared to the earlier review, however the main conclusions remain unchanged.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to determine the effects of tocolytics for uterine tachysystole or suspected fetal distress during labour. The clinical significance for some of the improvements in measures of fetal well-being with tocolytics is unclear. The sample sizes were too small to detect effects on neonatal morbidity, mortality or serious adverse effects. The majority of studies are from high-income countries in facilities with access to caesarean section,

which may limit the generalisability of the results to lower-resource settings, or settings where caesarean section is not available.

Implications for research

There is a need for well-designed and adequately powered randomised controlled trials examining the effects of tocolysis with different agents on fetus, neonate and mother.

It would be helpful if future studies collected data on clinically important maternal and neonatal outcomes to inform assessment of the benefits and harms of interventions, and were adequately powered to detect serious adverse events. In particular, data relating to neonatal morbidity and mortality and condition at birth are required to assess the clinical implications of tocolytic treatment. In the absence of clear evidence to support the use of tocolytics in cases of uterine tachysystole or fetal distress, trials could be placebo-controlled where possible. It would be useful to consider separately addressing two distinct management approaches: using tocolysis after the decision for emergency delivery has been made as an interim measure, versus using tocolysis as a treatment for tachysystole or fetal distress, without having committed to a specific mode of delivery.

ACKNOWLEDGEMENTS

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

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS) or the Department of Health.

The World Health Organization (WHO), Sebastian J Leathersich, Thach Son Tran and G Justus Hofmeyr retain copyright and all other rights in their respective contributions to the manuscript of this Review as submitted for publication.

Thanks to Nazie Amiransari for translating the [Kashanian 2006b](#) study.

REFERENCES

References to studies included in this review

Afschar 2004 {published data only}

Afschar P, Scholl W, Bader A, Bauer M, Winter R. A prospective randomised trial of atosiban versus hexoprenaline for acute tocolysis and intrauterine resuscitation. *BJOG: an international journal of obstetrics and gynaecology* 2004;**111**(4):316-8.

Briozzo 2007 {published data only}

Briozzo L, Martinez A, Nozar M, Fiol V, Pons J, Alonso J. Tocolysis and delayed delivery versus emergency delivery in cases of non-reassuring fetal status during labor. *Journal of Obstetrics and Gynaecology Research* 2007;**33**(3):266-73.

Kulier 1997 {published data only}

Kulier R, Gulmezoglu AM, Hofmeyr GJ. Betamimetics for fetal distress: a randomized trial. 14th Conference on Priorities in Perinatal Care in South Africa; 1995 March 7-10; South Africa. 1995:190-3.

* Kulier R, Gulmezoglu AM, Hofmeyr GJ, Van Gelderen CJ. Betamimetics in fetal distress: a randomised controlled trial. *Journal of Perinatal Medicine* 1997;**25**(1):97-100.

Magann 1993 {published data only}

* Magann EF, Cleveland RS, Dockery JR, Chauhan SP, Martin JN, Morrison JC. Acute tocolysis for fetal distress: terbutaline vs magnesium sulphate. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1993;**33**:362-4.

Magann EF, Cleveland RS, Dockery JR, Chauhan SP, Norman PH, Martin JN, et al. Acute tocolysis for fetal distress: terbutaline vs magnesium sulfate. 41st Annual Clinical Meeting of The American College of Obstetricians and Gynaecologists; 1993 May 3-6; USA. 1993:13.

Magann EF, Norman PF, Bass JD, Chauhan SP, Martin JN, Morrison JC. Acute tocolysis for suspected intrapartum fetal distress: maternal effects of terbutaline vs magnesium sulfate. *International Journal of Obstetric Anesthesia* 1995;**4**:140-4.

Pacheco 2006 {published data only}

Pacheco LD, Rosen M, Gei A, Zacharias N, Picans J, Vidal A, et al. Management of uterine hyperstimulation with concomitant use of oxytocin and terbutaline. *American Journal of Obstetrics and Gynecology* 2003;**189**(6 Suppl 1):S210.

* Pacheco LD, Rosen MP, Gei AF, Saade GR, Hankins GD. Management of uterine hyperstimulation with concomitant use of oxytocin and terbutaline. *American Journal of Perinatology* 2006;**23**(6):377-80.

Patriarco 1987 {published data only}

Patriarco MS, Viechnicki BM, Hutchinson TA, Klasko SK, Yeh SY. A study on intrauterine fetal resuscitation with terbutaline. *American Journal of Obstetrics and Gynecology* 1987;**157**:384-7.

Pullen 2007 {published data only}

NCT00185887. Nitroglycerin versus terbutaline for intrapartum fetal resuscitation. clinicaltrials.gov/ct2/show/NCT00185887 (first received 16 September 2005).

Pullen K, Taylor L, Waller S, Langen E, Druzin M, Riley E, et al. Terbutaline versus nitroglycerin for acute intrapartum fetal resuscitation. *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S30.

* Pullen KM, Riley ET, Waller SA, Taylor L, Caughey AB, Druzin ML, et al. Randomized comparison of intravenous terbutaline vs nitroglycerin for acute intrapartum fetal resuscitation. *American Journal of Obstetrics and Gynecology* 2007;**197**(4):414.e1-6.

Rudra 2007 {published data only}

Rudra T, Thirumal S, Naguleswaran K, Rudra S. Impact of nifedipine for acute tocolysis in acute fetal distress. 31st British International Congress of Obstetrics and Gynaecology; 2007 July 4-6; London, UK. 2007:58.

References to studies excluded from this review

Buhimschi 2002 {published data only}

Buhimschi CS, Buhimschi IA, Malinow AM, Weiner CP. Effects of sublingual nitroglycerin on human uterine contractility during the active phase of labor. *American Journal of Obstetrics and Gynecology* 2001;**185**(6):S209.

* Buhimschi CS, Buhimschi IA, Malinow AM, Weiner CP. Effects of sublingual nitroglycerin on human uterine contractility during the active phase of labor. *American Journal of Obstetrics and Gynecology* 2002;**187**(1):235-8.

Burke 1989 {published data only}

Burke MS, Porreco RP, Day D, Watson JD, Haverkamp AD, Orleans M, et al. Intrauterine resuscitation with tocolysis: an alternate month clinical trial. *Journal of Perinatology* 1989;**9**(3):296-300.

Campbell 1978 {published data only}

Campbell J, Anderson I, Chang A, Wood C. The use of ritodrine in the management of the fetus during the second stage of labour. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1978;**18**:110-3.

Chao 2002 {published data only}

Chao A, El-Sayed YY, Sapugay AM. Does nifedipine prevent the tachysystole associated with misoprostol induction?. *Journal of Maternal-Fetal & Neonatal Medicine* 2002;**11**(4):266-9.

Cilliers 2013 {published data only}

* Cilliers JBF, Schoon MG, Bam RH, Niemand I. A randomised clinical trial to determine the effect of beta-adrenergic blocking with propranolol on labour. *South African Journal of Obstetrics and Gynaecology* 2013;**19**(2):53-5.

Schoon MG, Cilliers JBF, Bam RH, Niemand I. A randomised clinical trial to determine the effect of beta-adrenergic blocking with propranolol on labour. 20th Conference on Priorities in Perinatal Care in Southern Africa; 2001 March 6-9; KwaZulu-Natal, South Africa. 2001.

Dunn 2016 {published data only}

ACTRN12615000319572. Does sildenafil reduce the risk of fetal distress in labour?. anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368057 (first received 9 April 2015).

Dunn L, Flenady V, Kumar S. Reducing the risk of fetal distress with sildenafil study (RIDSTRESS): a double-blind randomised control trial. *Journal of Translational Medicine* 2016;**14**(1):15. [MEDLINE: 26767411]

Ekblad 1988 {published data only}

Ekblad U, Erkkola R, Uotila P, Kanto J, Palo P. Ritodrine infusion at term: effects on maternal and fetal prostacyclin, thromboxane and prostaglandin precursor fatty acids. *Gynecologic and Obstetric Investigation* 1988;**25**:106-12.

Gerris 1980 {published data only}

Gerris J, Thiery M, Bogaert M, De Schaepdryver A. Randomized trial of two beta-mimetic drugs (ritodrine and fenoterol) in acute intra-partum tocolysis. *European Journal of Clinical Pharmacology* 1980;**18**:443-8.

Goeschen 1985 {published data only}

Goeschen K, Fuchs AR, Fuchs F, Rasmussen AB, Rehnstrom JV, Saling E. Effect of beta-mimetic tocolysis on cervical ripening and plasma prostaglandin F2alpha metabolite after endocervical application of prostaglandin E2. *Obstetrics & Gynecology* 1985;**65**:166-71.

Hidaka 1987 {published data only}

Hidaka A, Komatami M, Ikeda H, Kitanaka T, Okada K, Sugawa T. A comparative study of intrauterine fetal resuscitation by B-Stimulant and O2 Inhalation. *Asia-Oceania Journal of Obstetrics and Gynaecology* 1987;**13**(2):195-200.

Humphrey 1975 {published data only}

Humphrey M, Chang A, Gilbert M, Wood C. The effect of intravenous ritodrine on the acid-base status of the fetus during the second stage of labour. *British Journal of Obstetrics and Gynaecology* 1975;**82**:234-45.

Kashanian 2006a {published data only}

Kashanian M, Afshar A, Zarrin Z. A comparison between the effect of oxytocin only and oxytocin plus propranolol on the labor (a double blind randomized trial). *Journal of Maternal-Fetal and Neonatal Medicine* 2008;**21**(Suppl 1):73.

Kashanian M, Fekrat M, Zarrin Z, Ansari NS. A comparison between the effect of oxytocin only and oxytocin plus propranolol on the labor (a double blind randomized trial). *Journal of Obstetrics and Gynaecology Research* 2008;**34**(3):354-8.

* Kashanian M, Zarrin Z. A comparison between the effect of oxytocin only and oxytocin plus propranolol on the labor: a

double blind randomized trial. *Journal of the Kashan University of Medical Sciences* 2006;**10**(2):7-11.

Kashanian M, Zarrin Z. A comparison between the effect of oxytocin only and oxytocin plus propranolol on the labor (a double blind randomized trial). *Journal of Maternal-Fetal and Neonatal Medicine* 2010;**23**(S1):616-7.

Lipshitz 1976a {published data only}

Lipshitz J, Baillie P. The effects of the fenoterol hydrobromide (Partusisten) aerosol on uterine activity and the cardiovascular system. *British Journal of Obstetrics and Gynaecology* 1976;**83**:864-9.

Lipshitz 1976b {published data only}

Lipshitz J, Baillie P. Uterine and cardiovascular effects of beta2-selective sympathomimetic drugs administered as an intravenous infusion. *South African Medical Journal* 1976;**50**:1973-7.

Lipshitz 1976c {published data only}

Lipshitz J, Baillie P, Davey DA. A comparison of the uterine beta2-adrenoreceptor selectivity of fenoterol, hexoprenaline, ritodrine and salbutamol. *South African Medical Journal* 1976;**50**:1969-72.

Lipshitz 1984 {published data only}

Lipshitz J, Lipshitz EM. Uterine and cardiovascular effects of fenoterol and hexoprenaline in prostaglandin F2alpha-induced labor in humans. *Obstetrics & Gynecology* 1984;**63**:396-400.

Sharami 2012 {published data only}

Sharami SH, Milani F, Tofighi M, Salamt F, Dalil Heirati SF. Effect of oxytocin plus propranolol on the success of labor augmentation. *Journal of Guilan University of Medical Sciences* 2012;**82**:57-64.

Taylor 1990 {published data only}

Taylor AVG, Boland JC, MacKenzie IZ. Prostaglandin induced cervical ripening under tocolytic cover in primiparae: results of a double blind placebo controlled trial. *British Journal of Obstetrics and Gynaecology* 1990;**97**:827-31.

Torres 2001 {published data only}

Torres R, Santiago P, Rivera J, Adamsons K. Reduction of the duration of induced labor after blockade of myometrial adrenergic beta receptors with propranolol. *Journal of Perinatal Medicine* 2001;**29** Suppl 1(Pt 2):708.

Visser 1979 {published data only}

Visser AA, Prinsloo ST, Giesteira MVK. Suppression of uterine activity with salbutamol before caesarean section. *South African Medical Journal* 1979;**56**:1093-8.

Additional references

ACOG 2009

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No.106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and

general management principles. *Obstetrics & Gynecology* 2009;**114**(1):192-202.

Arias 1978

Arias F. Intrauterine resuscitation with terbutaline: a method for the management of acute intrapartum fetal distress. *American Journal of Obstetrics and Gynecology* 1978;**131**(1):39-43.

Bakker 2007

Bakker PC, Kurver PH, Kuik DJ, Van Geijn HP. Elevated uterine activity increases the risk of fetal acidosis at birth. *American Journal of Obstetrics and Gynecology* 2007;**196**(4):313.

Barber 2011

Barber E, Lundsberg L, Belanger K, Pettker C, Funai E, Illuzzi J. Contributing indications to the rising cesarean delivery rate. *Obstetrics & Gynecology* 2011;**118**(1):29-38.

Bloom 2006

Bloom SL, Spong CY, Thom E, Varner MW, Rouse DJ, Weininger S, et al. Fetal pulse oximetry and cesarean delivery. *New England Journal of Medicine* 2006;**355**(21):2195-202.

Brar 1988

Brar HS, Platt LD, DeVore GR, Horenstein J, Medearis AL. Qualitative assessment of maternal uterine and fetal umbilical artery blood flow and resistance in laboring patients by Doppler velocimetry. *American Journal of Obstetrics and Gynecology* 1988;**158**(4):952-6.

Crane 2001

Crane JM, Young DC, Butt KD, Bennett KA, Hutchens D. Excessive uterine activity accompanying induced labor. *Obstetrics & Gynecology* 2001;**97**(6):926-31.

De Heus 2008

De Heus R, Mulder EJ, Derks JB, Kurver PH, Van Wolfswinkel L, Visser GH. A prospective randomized trial of acute tocolysis in term labour with atosiban or ritodrine. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2008;**139**(2):139-45.

Dodd 2006

Dodd JM, Reid K. Tocolysis for assisting delivery at caesarean section. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: [10.1002/14651858.CD004944.pub2](https://doi.org/10.1002/14651858.CD004944.pub2)]

Fleischer 1987

Fleischer A, Anyaegbunam AA, Schulman H, Farmakides G, Randolph G. Uterine and umbilical artery velocimetry during normal labor. *American Journal of Obstetrics and Gynecology* 1987;**157**(1):40-3.

Garite 2000

Garite TJ, Dildy GA, McNamara H, Nageotte MP, Boehm FH, Dellinger EH, et al. A multicenter controlled trial of fetal pulse oximetry in the intrapartum management of nonreassuring fetal heart rate patterns. *American Journal of Obstetrics and Gynecology* 2000;**183**(5):1049-58.

Hanskin 2003

Hankins GD, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. *Obstetrics & Gynecology* 2003;**102**(3):628-36.

Higgins 2011

Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Hubinont 2011

Hubinont C, Debieve F. Prevention of preterm labour: 2011 update on tocolysis. *Journal of Pregnancy* 2011;**2011**:941057.

Ingemarsson 1985

Ingemarsson I, Arulkumaran S, Ratnam SS. Single injection of terbutaline in term labor. I. Effect on fetal pH in cases with prolonged bradycardia. *American Journal of Obstetrics and Gynecology* 1985;**153**(8):859-65.

Kashanian 2006b

Kashanian M, Zarrin Z. A comparison between the effect of oxytocin only and oxytocin plus propanolol on the labor: a double blind randomized trial. *Journal of the Kashan University of Medical Sciences* 2006;**10**(2):7-11.

Lumbiganon 2010

Lumbiganon P, Laopaiboon M, Gülmezoglu AM, Souza JP, Taneepanichskul S, Ruyan P, et al. Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007-08. *Lancet* 2010;**375**(9713):490-9.

McNamara 1995

McNamara H, Johnson N. The effect of uterine contractions on fetal oxygen saturation. *BJOG: an international journal of obstetrics and gynaecology* 1995;**102**(8):644-7.

Peebles 1994

Peebles DM, Spencer JA, Edwards AD, Wyatt JS, Reynolds EO, Cope M, et al. Relation between frequency of uterine contractions and human fetal cerebral oxygen saturation studied during labour by near infrared spectroscopy. *BJOG: an international journal of obstetrics and gynaecology* 1994;**101**(1):44-8.

Pullen 2000

Pullen KM, Riley ET, Waller SA, Taylor L, Caughey AB, Druzin ML, et al. Randomized comparison of intravenous terbutaline vs nitroglycerin for acute intrapartum fetal resuscitation. *American Journal of Obstetrics and Gynecology* 2007;**197**(4):414.e1-.e6.

RCOG 2008

National Collaborating Centre for Women's and Children's Health (UK). *Induction of Labour*. London: RCOG Press, 2008.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. *Review Manager 5 (RevMan 5)*. Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sheybany 1982

Sheybany S, Murphy JF, Evans D, Newcombe RG, Pearson JF. Ritodrine in the management of fetal distress. *BJOG: an international journal of obstetrics and gynaecology* 1982;**89**(9):723-6.

Simpson 2005

Simpson KR, James DC. Efficacy of intrauterine resuscitation techniques in improving fetal oxygen status during labor. *Obstetrics & Gynecology* 2005;**105**(6):1362-8.

Simpson 2007

Simpson K. Intrauterine resuscitation during labor: review of current methods and supportive evidence. *Journal of Midwifery & Women's Health* 2007;**52**(3):229-37.

Simpson 2008

Simpson KR, James DC. Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns. *American Journal of Obstetrics and Gynecology* 2008;**199**(1):34.e1-e5.

Stjernholm 2010

Stjernholm YV, Petersson K, Eneroth E. Changed indications for cesarean sections. *Acta Obstetrica et Gynecologica Scandinavica* 2010;**89**(1):49-53.

Vigil-De Gracia 2000

Vigil-De Gracia P, Simiti E, Lora Y. Intrapartum fetal distress and magnesium sulfate. *International Journal of Gynecology and Obstetrics* 2000;**68**(1):3-6.

von Katterfeld 2011

von Katterfeld B, Li J, McNamara B, Langridge AT. Perinatal complications and cesarean delivery among foreign-born and Australian-born women in Western Australia, 1998-2006. *International Journal of Gynecology and Obstetrics* 2012;**116**(2):153-7.

WHO 2011

World Health Organization. WHO Recommendations for Induction of Labour. Geneva: World Health Organization, 2011.

References to other published versions of this review

Kulier 2000

Kulier R, Hofmeyr GJ. Tocolytics for suspected intrapartum fetal distress. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: [10.1002/14651858.CD000035](https://doi.org/10.1002/14651858.CD000035)]

Tran 2012

Tran TS, Kulier R, Hofmeyr GJ. Acute tocolysis for uterine tachysystole or suspected fetal distress. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: [10.1002/14651858.CD009770](https://doi.org/10.1002/14651858.CD009770)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Afschar 2004

Methods	2-arm randomised pilot study
Participants	26 women were randomised from a total of 1431 enrolled women.
	Inclusion criteria <p>≥ 38 weeks of gestation and in labour with severe fetal bradycardia (FHR < 80 bpm for more than 3 minutes) requiring intrauterine resuscitation.</p> <p>Whilst singleton pregnancy and cephalic presentation were not specifically listed as inclusion criteria, only such women were enrolled at the time of consent.</p>
	Exclusion criteria <p>Serious maternal diseases (pre-eclampsia, maternal hypertension, HELLP syndrome, metabolic diseases) or fetal or placental abnormalities (IUGR, fetal anomalies)</p>
Interventions	Group 1 <p>IV atosiban (6.75 mg diluted in 4.9 mL of physiological saline) administered over 1 minute</p> <p>(n = 13)</p> Group 2

Acute tocolysis for uterine tachysystole or suspected fetal distress (Review)

Afschar 2004 (Continued)

IV hexoprenaline (5 µg diluted in 10 mL of physiological saline) administered over 5 minutes

(n = 13)

All women had continuous FHR monitoring during the active phase of labour.

Outcomes	<p>Specified endpoints</p> <ul style="list-style-type: none"> Cessation of uterine contractions and resumption of uterine contractions as determined by FHR monitoring <p>Primary outcomes</p> <ul style="list-style-type: none"> Apgar scores at 1, 5 and 10 minutes Umbilical artery pH values Admission to NICU <p>Secondary outcomes</p> <ul style="list-style-type: none"> Maternal side effects (tachycardia, hypotension, palpitations) Maternal BP and heart rate 10 minutes after drug administration
Notes	<p>No power calculation was performed.</p> <p>The study was undertaken from October 2000 - May 2001.</p> <p>Atosiban was provided by Ferring Pharmaceuticals. The authors reported no personal financial support; there was no comment on other potential conflicts of interest.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation was performed by treatment boxes" - it is unclear what "treatment boxes" are.
Allocation concealment (selection bias)	Low risk	Treatment boxes were held at the University of Graz.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information on blinding was not provided. The two medications being compared were administered over different time periods so it may not have been possible to blind women or some clinical staff.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were reported for all randomised participants and there do not appear to be differences in populations or missing outcomes.
Selective reporting (reporting bias)	Low risk	The Apgar score cut-off of < 7 was not prespecified, however this is a reasonable cut-off to use. Some non-prespecified outcomes were used, however they were considered to be clinically relevant and reasonable outcomes. All outcomes described in the study methods were reported.
Other bias	Low risk	Atosiban was supplied by Ferring Pharmaceuticals, but authors report no other personal financial supports. No conflicts of interest were reported.

Afschar 2004 (Continued)

The sample size is very small in this trial.

Briozzo 2007

Methods	2-arm randomised controlled trial
Participants	<p>390 women were randomised.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Term singleton pregnancy • Cephalic presentation • In labour with cervical dilatation > 3 cm • Uterine contraction pattern of 3-5 in 10 minutes • NRFHT on electronic FHR and contraction monitoring • Consent <p>Though not stated as inclusion criteria, there were functional inclusion criteria due to the fact that only women who met certain criteria had electronic FHR monitoring (which was a requirement of inclusion). These were women who had at least 1 of: previous perinatal demise, age > 40, pathologies during pregnancy, alterations in fetal growth and development, dystocic labour, > 41/40, PROM or antepartum haemorrhage in the third trimester, effectively making these inclusion criteria.</p> <p>Non-reassuring fetal status was diagnosed according to the following definitions of FHR patterns from the National Institute of Child and Human Development.</p> <ol style="list-style-type: none"> 1. DIP II (late decelerations of the FHR) in at least 3 consecutive contractions. 2. Fetal bradycardia (< 110 beats/minute) or fetal tachycardia (> 160 beats/minute) over 10 minutes, not improving with the mother's change of position. 3. Absent (undetectable) and minimal FHR variability (≤ 5 beats/minute), 10-minute segments, when no drugs that may decrease heart rate variability were administered, and the situation was not improved with external cephalic stimulation. 4. Prolonged deceleration of FHR ≥ 15 beats/minute below baseline, lasting 2 minutes, but < 10 minutes from onset to return to baseline, and variable decelerations of FHR below the baseline ≥ 15 beats/minute lasting ≥ 15 seconds and < 2 minutes from onset to return to baseline. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Maternal cardiopathy • Hyperthyroidism • Placental abruption or placental accidents • Hyperstimulation with oxytocin • Reversible cause of NRFHT (uterine hyperstimulation, maternal hypotension due to analgesia)
Interventions	<p>Intervention</p> <p>FIR with fenoterol bromhydrate (0.5 mg in 500 mL of saline given IV at 0.1 mg/minute then titrated according to response). Titration aimed to decrease uterine contractility without increasing maternal HR by more than 30 beats/minute or decreasing BP by more than 30 mmHg systolic or 15 mmHg diastolic.</p> <p>10 minutes after implementation of FIR, 3 possibilities were evaluated: (i) improvement of FHR patterns and decreased uterine contractility; (ii) fetal situation unchanged; and/or (iii) worsening of the clinical situation (another parameter is added, severe bradycardia, etc.).</p> <p><i>Ineffective FIR</i></p>

Briozzo 2007 (Continued)

If the fetal situation was unchanged or had worsened, FIR was considered as ineffective and emergency delivery was performed, usually by caesarean section. In some cases, immediate forceps delivery was possible.

Effective FIR

If the fetal situation improved, FIR was considered as effective and utero-inhibition was maintained for 20 minutes, under permanent surveillance. Then, caesarean section was performed. In a few cases forceps delivery was more appropriate because of the fetal head station.

Comparison

Emergency delivery, usually by caesarean section, however instrumental delivery was performed if it was more appropriate.

(n = 197)

Outcomes	Primary outcomes <ul style="list-style-type: none">• Umbilical artery pH < 7.10 or base excess ≤ 12• Admission to NICU, which was based on 1 or more of:<ul style="list-style-type: none">◦ alterations of the central nervous system;◦ haemodynamic alterations;◦ alterations of the respiratory system. Secondary outcomes <ul style="list-style-type: none">• Apgar scores at 1 and 5 minutes• “Maternal health” (intrapartum haemorrhage, admission to ICU or intermediate care unit, number of days of hospitalisation postpartum, type of anaesthesia during caesarean)	
Notes	<p>This study specifically excluded women who had been diagnosed with uterine hyperstimulation.</p> <p>The study was undertaken from 1 January 2001 - 1 June 2004.</p> <p>The authors did not comment on either funding sources or conflicts of interest.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The random allocation of cases was generated by a computer program, with randomly permuted blocks of 20."
Allocation concealment (selection bias)	Low risk	"The sequence, stored in closed envelopes, was opened following the pre-established order."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Significant difference in intervention (medication) and control (emergency delivery) precludes blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>It is not stated whether assessors of maternal outcomes were blinded to the allocation.</p> <p>Neonatologists were blinded to the intervention, and it is specifically stated that neonatologists assessed the Apgar score. It is presumed, though not specifically stated, that neonatologists assessed other neonatal outcomes.</p>

Briozzo 2007 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data analysed and reported for all randomised participants on an intention-to-treat basis. There were no significant differences between populations in each arm.
Selective reporting (reporting bias)	High risk	<ul style="list-style-type: none"> The thresholds for some outcomes (e.g. Apgar scores) were not reported in the Methods section, though the cut-offs used are reasonable. The base excess cut-off is stated as ≤ 12 in the primary outcome section, but is reported as < -12, which may constitute outcome switching. The study protocol was not able to be located on ICTRP. Maternal outcomes are reported in the text but not in the tables – some were reported as not significant but without data presented. The discussion mentions a difference in caesarean rate, but data were not presented. A special analysis was undertaken comparing a subgroup of women in the intervention group who worsened against the control group. This was not prespecified. It is not explained why this was conducted.
Other bias	High risk	<p>FHR monitoring was only used in a specific subgroup of women who were at a higher risk, which effectively creates an undisclosed inclusion criteria.</p> <p>The authors' conflicts of interest were not reported.</p>

Kulier 1997

Methods	Randomised controlled trial
Participants	<p>37 women were enrolled.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> GA > 35/40 In active labour Decision made to deliver by caesarean section for fetal distress already made by attending doctor Persistent FHR abnormalities consistent with fetal distress <p>Exclusion criteria</p> <ul style="list-style-type: none"> Significant antepartum haemorrhage Cardiac disease Gross fetal abnormalities Betamimetics in use for another indication already
Interventions	<p>Intervention</p> <p>IV hexoprenaline (10 µg) as an injection over 5 minutes</p> <p>(n = 17)</p> <p>Control</p> <p>Not stated</p> <p>(n = 20)</p>
Outcomes	<p>Prespecified outcomes</p> <ul style="list-style-type: none"> Cord blood pH and base excess Apgar scores at 1 and 5 minutes

Kulier 1997 (Continued)

- Need for neonatal resuscitation
- Need for NICU admission

Outcomes not prespecified

- FHR pattern improved
- Presence of meconium
- Cord around neck
- Stillbirth
- Randomisation-delivery interval
- Blood loss
- Birthweight

Notes

The dates of this study were not reported.

The authors did not comment on either funding sources or conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done by computer generated random numbers in blocks of ten."
Allocation concealment (selection bias)	Low risk	"They were then randomised by numbered, sealed opaque envelopes to hexoprenaline or control groups."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not discussed, however it is unlikely that participants could have been blinded without a placebo injection (which is not discussed).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Interpretation of FHR tracings was blinded, but blinding for other outcomes not discussed
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete data for some outcomes, with the reason for this not addressed in the study. There were no differences between populations, and both groups were affected by some missing data points.
Selective reporting (reporting bias)	Low risk	The authors reported on all outcomes described in the methods of the study.
Other bias	Unclear risk	The management of the comparison group was not clearly defined, and the cut-off values for outcomes were not prespecified. The authors' conflicts of interest were not reported.

Magann 1993

Methods	2-arm randomised controlled trial
Participants	46 women were randomised.
Inclusion criteria	
<ul style="list-style-type: none"> • Women in active labour who develop signs of fetal distress: 	

Magann 1993 (Continued)

- diminished variability and variable decelerations of < 60 bpm lasting > 60 seconds with a slow return to baseline;
- acute persistent bradycardia of < 120 bpm for > 10 minutes;
- persistent late decelerations with little or no variability.
- Failure of conventional approaches to manage fetal distress, including oxytocin discontinuation, fluid bolus, position change, maternal oxygen or amnioinfusion
- Decision made to deliver by caesarean section

All women had continuous FHR monitoring by fetal scalp electrode and intrauterine pressure transducers.

Exclusion criteria

Maternal conditions that could compromise haemodynamic stability including placental abruption, maternal haemorrhage or severe pre-eclampsia

Interventions	<p>Group 1</p> <p>Subcutaneous terbutaline (250 µg)</p> <p>(n = 23)</p> <p>Group 2</p> <p>IV bolus of magnesium sulphate (4 g) over 10 minutes</p> <p>(n = 23)</p> <p>In both groups caesarean section was commenced within 15 minutes of administration of treatment.</p>
Outcomes	<ul style="list-style-type: none"> • Change in uterine activity measured by Montevideo units during the 10 minutes before and after drug administration • FHR response to drug administration (unchanged or improved) • Umbilical artery pH at time of delivery <p>1 report included post-hoc outcomes relating to the woman, which were reported as continuous variables during induction of anaesthesia for caesarean section with either general anaesthetic, subarachnoid block or epidural (mean +/- S.D.)</p> <ul style="list-style-type: none"> • Mean arterial pressure • Heart rate • Mean oxygen saturation • Volume of IV fluids received intraoperatively • Requirement for vasopressors • Mean urine output during surgery • Preoperative and postoperative haematocrit
Notes	<p>Included 3 reports of 1 study</p> <p>This study was supported in part by the Vicksburg Hospital Medical Foundation.</p> <p>The authors did not comment on other funding sources or on conflicts of interest.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random group assignment was assured by card selection from sealed, opaque envelopes with group assignment derived from a random number table."

Magann 1993 (Continued)

Allocation concealment (selection bias)	Low risk	“Random group assignment was assured by card selection from sealed, opaque envelopes with group assignment derived from a random number table.”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded due to different route of drug administration. No discussion of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“The investigator who reviewed the monitor strip of each study subject for fetal heart rate response and uterine activity quantitation was blinded to details of women's management and specific medication utilized.” Blinding for other outcome assessment was not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all 46 enrolled women for all prespecified outcomes.
Selective reporting (reporting bias)	Low risk	Results were reported for all prespecified outcomes.
Other bias	Low risk	Not detected This study was supported in part by the Vicksburg Hospital Medical Foundation. The authors' conflicts of interest were not reported.

Pacheco 2006

Methods	Randomised controlled trial
Participants	<p>30 women were randomised, 15 to each group. 1 woman randomised to the control group was excluded post-randomisation at the woman's request.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Singleton term pregnancy • Active labour (regular contractions and cervical dilatation of 3 cm in nullips and 4 cm in multips) • Requiring oxytocin augmentation • Uterine hyperstimulation: <ul style="list-style-type: none"> ◦ uterine hyperstimulation was diagnosed if any of the following patterns were present for at least 20 minutes: more than 5 contractions in 10 minutes (tachysystole), basal uterine tone > 20 mmHg in women with an intrauterine pressure catheter (hypertonus), more than 250 Montevideo units in 10 minutes as measured by an intrauterine pressure catheter, contractions lasting more than 90 seconds (tetany), or the presence of contractions in couplets or triplets before returning to baseline resting tone (polysystole) • Uterine hyperstimulation did not resolve spontaneously within 20 minutes of observation <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Poorly controlled diabetes; maternal cardiopulmonary disease; polyhydramnios • Non-reassuring fetal monitoring (repetitive late decelerations, severe variable decelerations, fetal tachycardia with loss of variability, fetal bradycardia) • Chorioamnionitis

Pacheco 2006 (Continued)

- Maternal tachycardia > 120 bpm

Interventions	<p>2 management protocols were compared in this study.</p> <p>Intervention</p> <p>Subcutaneous terbutaline (250 µg, up to 3 doses in total) with continuation of the oxytocin infusion. Additional doses of terbutaline were administered at 15 minute intervals if hyperstimulation had not resolved. If hyperstimulation persisted after 3 doses, oxytocin was discontinued.</p> <p>(n = 15)</p> <p>Comparison</p> <p>Discontinuation of the oxytocin infusion with no tocolytic administered. If the hyperstimulation resolved in < 30 minutes, the infusion was recommenced at half the original dose. If the hyperstimulation persisted beyond 30 minutes, the infusion was recommenced at 2 mIU/minute.</p> <p>(n = 14)</p>
Outcomes	<ul style="list-style-type: none"> • Time to resolution of hyperstimulation • Recurrence of hyperstimulation • Chorioamnionitis • Caesarean section • Apgar scores at 1 and 5 minutes
Notes	<p>Women with non-reassuring fetal monitoring were excluded.</p> <p>This study compared 2 different treatment protocols, rather than directly comparing 2 different treatments.</p> <p>The dates of this study were not reported.</p> <p>The authors did not comment on either funding sources or conflicts of interest.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Simple randomisation" using a "computer-based program"
Allocation concealment (selection bias)	Low risk	Sealed envelope given to women
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported for participants or personnel, and the difference in protocols was likely to be obvious to women and clinicians.
Blinding of outcome assessment (detection bias) All outcomes	High risk	"All women observed until delivery by the primary investigator", no blinding of assessors described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not detected. Data were reported for all patients who consented to be involved in the study for all outcomes.
Selective reporting (reporting bias)	Unclear risk	There were no significant differences in women's characteristics between groups.

Pacheco 2006 (Continued)

		1 woman randomised to the control group withdrew consent after randomisation and was excluded.
		Outcomes were not prespecified.
Other bias	Low risk	Not detected
		The authors' conflicts of interest were not reported.

Patriarco 1987

Methods	Randomised controlled trial
Participants	<p>20 women were randomised.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Women in labour with signs of fetal distress (repetitive late decelerations or severe variable decelerations on FHR monitoring) • Women in whom conservative management (maternal repositioning, maternal oxygen mask and/or cessation of oxytocin infusion if in use) failed to improve fetal heart trace had fetal scalp blood samples obtained. if the pH was < 7.25, the woman was recruited, consented and randomised <p>Exclusion criteria</p> <p>None documented</p> <p>7 women who met the clinical criteria for inclusion were excluded because fetal scalp pH was not obtained, or because immediate intervention was required precluding terbutaline administration. They were presented as case reports.</p>
Interventions	<p>Intervention</p> <p>Subcutaneous terbutaline (250 µg) whilst preparations were being made for urgent delivery (n = 11)</p> <p>Comparison</p> <p>No medication given (n = 9)</p> <p>All participants were delivered by urgent caesarean section.</p>
Outcomes	<p>Outcomes were not specifically prespecified, however the following can be identified in the methods section.</p> <ul style="list-style-type: none"> • FHR monitoring continued after intervention (or nothing) given • Blood samples obtained from umbilical artery at time of delivery for pH level • All neonates evaluated by paediatrician or neonatologist in the delivery room; Apgar scores were given
Notes	<p>7 individual cases were also presented, who were not included because fetal scalp blood samples were not obtained prior to the administration of terbutaline. It is not clear if these women were randomised or how else they differ from the main study group, and they have therefore been excluded from the meta-analysis.</p> <p>This study was performed from January 1984-December 1985.</p> <p>The authors did not comment on either funding sources or conflicts of interest.</p>

Patriarco 1987 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"She was randomly assigned to the study or control group by randomly generated numbers."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not discussed
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel as no placebo given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all randomised women, with no differences in characteristics between the 2 groups.
Selective reporting (reporting bias)	Low risk	Not detected. Results were reported for all prespecified outcomes.
Other bias	Low risk	Outcomes not prespecified The authors' conflicts of interest were not reported.

Pullen 2007

Methods	2-arm randomised controlled trial
Participants	<p>110 women were randomised from 956 enrolled women.</p> <p>Inclusion criteria</p> <p>Women with a singleton pregnancy between 32 and 42 weeks' gestation who were admitted in active labour or for induction of labour were enrolled. Those with NRFHT on FHR monitoring received conservative management including maternal repositioning, IV fluids, oxygen administration and cessation of augmentation/induction medications. The option of amnioinfusion was left to the doctor. If these failed to resolve the NRFHT, women were randomised.</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> Maternal: <ul style="list-style-type: none"> pre-eclampsia, chronic hypertension, cardiac disease, placental abruption, insulin-dependent diabetes mellitus, hyperthyroidism, age < 18 years or previous caesarean section Fetal: <ul style="list-style-type: none"> IUGR, multiple gestation, fetal anomalies that are incompatible with life <p>Women were also excluded if the only indication of fetal distress was fetal tachycardia with reduced variability in the context of chorioamnionitis.</p> <p>If, after the study drug, further episodes of NRFHT occurred, management was at the discretion of the treating team.</p>

Pullen 2007 (Continued)

Interventions	Intervention 1 IV terbutaline (250 µg) (n = 57) Intervention 2 IV nitroglycerin (400 µg) (n = 53)	
Outcomes	Primary outcome <ul style="list-style-type: none">• Composite measure of successful intrauterine fetal resuscitation: complete resolution of NRFHT within 10 minutes, no recurrence of the NRFHT and no administration of additional tocolytic within 30 minutes, and no operative delivery for NRFHT within 1 hour or drug administration	
Notes	<p>Non-reassuring fetal status was defined as prolonged deceleration (FHR < 100 bpm for > 2 minutes), severe variable deceleration (decreased in FHR to ≤ 70 bpm for ≥ 60 seconds but < 2 minutes), late deceleration (gradual decrease in FHR with nadir occurring after the peak of the contraction) or tachycardia with reduced variability in the absence of clinical signs of chorioamnionitis.</p> <p>Significantly more women who were assigned randomly to the terbutaline group had oligohydramnios on admission (defined as an amniotic fluid index of 5 cm with intact membranes). This was discussed in the context of the paper with a third reviewer (GJH), and it was agreed that this is likely a chance occurrence based on an appropriately described randomisation process and the fact that the other parameters are well balanced.</p> <p>This study was performed from October 2003 - June 2006.</p> <p>The authors did not comment on either funding sources or conflicts of interest.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation chart created using a random numbers table and concealed in the medication supply room.
Allocation concealment (selection bias)	Low risk	“prepared concealed randomisation chart that was located in the medication supply room” “study drug assignment was available only to the L&D nurse who prepared the medication”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Obstetrician and women blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Fetal heart tracings reviewed by blinded assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women received their assigned treatment and were included in the analysis. Outcome data are available for all women for all outcomes with the exception of umbilical artery pH, however the amount of missing data are similar between groups (33% missing in the terbutaline group compared to 30% missing in the nitroglycerin group).

Pullen 2007 (Continued)

Selective reporting (reporting bias)	Low risk	Many outcomes were reported that were not prespecified, however they were reasonable in the context of the trial question. Prespecified outcomes were reported for all included women.
Other bias	Low risk	Not detected The authors' conflicts of interest were not reported.

Rudra 2007

Methods	Randomised head-to-head trial	
Participants	Women with severe CTG abnormalities for whom a decision had been made to perform category 1 caesarean section	
Interventions	Group 1: sublingual nifedipine (n = 36) Group 2: IV salbutamol (n = 39)	
Outcomes	All reported as percentages in each group only, and not prespecified <ul style="list-style-type: none"> • Maternal tachycardia (no definition) • Maternal hypotension (no definition) • Improvement in CTG abnormality • Apgar score (reported as "good") • Neonatal requirement for postnatal ventilatory support • Anaesthetic complications • Postoperative uterine hypotonia 	
Notes	Abstract only. Efforts were made to contact the primary author to obtain further information regarding the study and its outcomes, however there was no response provided. This study was performed from 2004 - 2005. The authors did not comment on either funding sources or conflicts of interest.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Process for randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described

Acute tocolysis for uterine tachysystole or suspected fetal distress (Review)

Rudra 2007 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided in order for us to assess this
Selective reporting (reporting bias)	Unclear risk	Risk of reporting bias is unclear as the study outcomes were not clearly pre-specified.
Other bias	Unclear risk	Not able to be assessed The authors' conflicts of interest were not reported

BP: blood pressure

bpm: beats per minute

CTG: cardiotocograph

FIR: fetal intrauterine resuscitation

FHR: fetal heart rate

GA: gestational age

HELLP: haemolysis elevated liver enzymes and low platelets

IV: intravenous

ICU: intensive care unit

ICTRP: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

IUGR: intrauterine growth restriction

NICU: neonatal intensive care unit

NRFHT: non-reassuring fetal heart trace

PROM: premature rupture of membranes

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Buhimschi 2002	Ineligible participants (women in active labour with normal progression of labour, without either tachysystole or fetal distress)
Burke 1989	Quasi-randomised trial with intervention assigned on an alternating month basis
Campbell 1978	Routine tocolysis in the second stage of labour, rather than being used for either fetal distress or tachysystole
Chao 2002	Prophylactic tocolysis in women undergoing induction of labour. Excluded women with uterine tachysystole or fetal distress
Cilliers 2013	Ineligible participants (women with prolonged active phase of labour), no tocolytic used (intervention group received propranolol)
Dunn 2016	Prophylactic use of sildenafil in women in labour without evidence of either fetal distress or uterine tachysystole
Ekblad 1988	Biochemical study in women undergoing elective caesarean section at term who had neither fetal distress nor uterine tachysystole
Gerris 1980	Tocolysis in nulliparous women in the first stage of a normal labour with neither uterine tachysystole nor fetal distress
Goeschen 1985	Ineligible population (women undergoing induction of labour with prostaglandin gel were treated with β -mimetics prophylactically)

Acute tocolysis for uterine tachysystole or suspected fetal distress (Review)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Hidaka 1987	Unclear whether participants were randomised
Humphrey 1975	Tocolysis in women with uncomplicated pregnancies and a normal second stage of labour. Excludes women with suspected fetal distress
Kashanian 2006a	Propanolol used (no tocolytic), and alternate allocation rather than randomisation
Lipshitz 1976a	Ineligible participants (women with elective induction of labour and without uterine tachysystole or fetal distress)
Lipshitz 1976b	Ineligible participants (women with elective induction of labour and without uterine tachysystole or fetal distress)
Lipshitz 1976c	Ineligible participants (women with elective induction of labour and without uterine tachysystole or fetal distress)
Lipshitz 1984	Observational study design
Sharami 2012	Ineligible participants (women in active labour with failure to progress), no tocolytic used (intervention group received propanolol)
Taylor 1990	Ineligible participants (women undergoing induction of labour for hypertension or prolonged pregnancy)
Torres 2001	Ineligible participants (women undergoing induction of labour)
Visser 1979	Imbalance between groups and a large number of unexplained exclusions suggests no effective randomisation

DATA AND ANALYSES

Comparison 1. Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fetal or neonatal mortality	2	57	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.55]
2 Five-minute Apgar score < 7	2	55	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.57]
3 Fetal heart rate tracing not improved	2	43	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.08, 0.95]

Analysis 1.1. Comparison 1 Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 1 Fetal or neonatal mortality.

Analysis 1.2. Comparison 1 Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 2 Five-minute Apgar score < 7.

Analysis 1.3. Comparison 1 Selective β_2 -adrenergic agonist versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 3 Fetal heart rate tracing not improved.

Comparison 2. IV atosiban versus IV hexoprenaline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death or severe morbidity	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.50]
2 Fetal or neonatal mortality	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Caesarean delivery	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.50]
4 Five-minute Apgar score < 7	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Umbilical artery pH	1	26	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.05, 0.05]
6 Abnormal fetal heart rate tracing	1	26	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 67.51]
7 Maternal side effects (tachycardia or palpitations)	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.1 [0.01, 0.67]
8 Admission to NICU	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.50]

Analysis 2.1. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 1 Perinatal death or severe morbidity.

Analysis 2.2. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 2 Fetal or neonatal mortality.

Analysis 2.3. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 3 Caesarean delivery.

Analysis 2.4. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 4 Five-minute Apgar score < 7.

Analysis 2.5. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 5 Umbilical artery pH.

Analysis 2.6. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 6 Abnormal fetal heart rate tracing.

Study or subgroup	IV atosiban n/N	IV hexo- prenaline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.69(P=0.49)					
Favours IV atosiban 0.01 0.1 1 10 100 Favours IV hexoprenaline					

Analysis 2.7. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 7 Maternal side effects (tachycardia or palpitations).

Study or subgroup	IV atosiban n/N	IV hexo- prenaline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Afschar 2004	1/13	10/13		100%	0.1[0.01,0.67]
Total (95% CI)	13	13		100%	0.1[0.01,0.67]
Total events: 1 (IV atosiban), 10 (IV hexoprenaline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.37(P=0.02)					
Favours IV atosiban 0.01 0.1 1 10 100 Favours IV hexoprenaline					

Analysis 2.8. Comparison 2 IV atosiban versus IV hexoprenaline, Outcome 8 Admission to NICU.

Study or subgroup	IV atosiban n/N	IV hexo- prenaline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Afschar 2004	0/13	1/13		100%	0.33[0.01,7.5]
Total (95% CI)	13	13		100%	0.33[0.01,7.5]
Total events: 0 (IV atosiban), 1 (IV hexoprenaline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
Favours IV atosiban 0.01 0.1 1 10 100 Favours IV hexoprenaline					

Comparison 3. IV fenoterol bromhydrate versus emergency delivery

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Caesarean delivery	1	390	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.04, 1.22]
2 Five-minute Apgar score < 7	1	390	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.35, 4.68]
3 Umbilical artery pH < 7.1	1	390	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.44, 1.05]
4 Umbilical cord blood base excess < -12	1	390	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.46, 1.00]
5 Admission to NICU	1	390	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.27, 0.81]

Analysis 3.1. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 1 Caesarean delivery.

Analysis 3.2. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 2 Five-minute Apgar score < 7.

Analysis 3.3. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 3 Umbilical artery pH < 7.1.

Analysis 3.4. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 4 Umbilical cord blood base excess < -12.

Analysis 3.5. Comparison 3 IV fenoterol bromhydrate versus emergency delivery, Outcome 5 Admission to NICU.

Comparison 4. IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fetal or neonatal mortality	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.55]
2 Five-minute Apgar score < 7	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.01, 4.57]
3 Umbilical artery pH < 7.2	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.30, 1.35]
4 Fetal heart rate tracing not improved	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.21, 0.88]
5 Meconium-stained amniotic fluid	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.09, 0.83]
6 Umbilical cord blood base excess < -10	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.13, 1.37]
7 Admission to NICU	1	37	Risk Ratio (M-H, Fixed, 95% CI)	3.5 [0.15, 80.71]

Analysis 4.1. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 1 Fetal or neonatal mortality.

Analysis 4.2. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 2 Five-minute Apgar score < 7.

Analysis 4.3. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 3 Umbilical artery pH < 7.2.

Analysis 4.4. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 4 Fetal heart rate tracing not improved.

Analysis 4.5. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 5 Meconium-stained amniotic fluid.

Analysis 4.6. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 6 Umbilical cord blood base excess < -10.

Analysis 4.7. Comparison 4 IV hexoprenaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 7 Admission to NICU.

Comparison 5. Subcutaneous terbutaline versus IV magnesium sulphate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Umbilical artery pH < 7.2	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.07, 1.23]
2 Resolution of fetal distress on fetal heart rate tracing	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.97, 1.77]

Analysis 5.1. Comparison 5 Subcutaneous terbutaline versus IV magnesium sulphate, Outcome 1 Umbilical artery pH < 7.2.

Analysis 5.2. Comparison 5 Subcutaneous terbutaline versus IV magnesium sulphate, Outcome 2 Resolution of fetal distress on fetal heart rate tracing.

Comparison 6. Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Caesarean delivery	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.68, 4.45]
2 Five-minute Apgar score < 7	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Umbilical artery pH < 7.0	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Time to resolution of uterine hy- perstimulation	1	28	Mean Difference (IV, Fixed, 95% CI)	-25.19 [-39.96, -10.42]
5 Recurrence of hyperstimulation after initial resolution	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.15, 1.77]

Analysis 6.1. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 1 Caesarean delivery.

Analysis 6.2. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 2 Five-minute Apgar score < 7.

Study or subgroup	Terbutaline with oxytocic n/N	Cessation of oxytocic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Pacheco 2006	0/15	0/13			Not estimable

Analysis 6.3. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 3 Umbilical artery pH < 7.0.

Analysis 6.4. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 4 Time to resolution of uterine hyperstimulation.

Analysis 6.5. Comparison 6 Subcutaneous terbutaline with continuation of oxytocic infusion versus cessation of oxytocic infusion without tocolytic, Outcome 5 Recurrence of hyperstimulation after initial resolution.

Comparison 7. Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fetal or neonatal mortality	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Five-minute Apgar score < 7	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 3.08]
3 Umbilical artery pH	1	20	Mean Difference (IV, Fixed, 95% CI)	0.08 [0.06, 0.10]
4 Abnormal FHR	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.33, 0.98]
5 No improvement in FHR	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.03, 0.59]

Analysis 7.1. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 1 Fetal or neonatal mortality.

Analysis 7.2. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 2 Five-minute Apgar score < 7.

Analysis 7.3. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 3 Umbilical artery pH.

Analysis 7.4. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 4 Abnormal FHR.

Analysis 7.5. Comparison 7 Subcutaneous terbutaline versus no tocolytic agent, whilst awaiting emergency delivery, Outcome 5 No improvement in FHR.

Comparison 8. IV terbutaline versus IV nitroglycerin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean delivery	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.68, 1.36]
2 Five-minute Apgar score < 7	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Umbilical artery pH < 7.0	1	75	Risk Ratio (M-H, Fixed, 95% CI)	4.87 [0.24, 98.18]
4 Uterine tachysystole 10 minutes after drug	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 0.70]
5 Need for repeat dose of tocolytic	1	110	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.57, 2.70]
6 Successful fetal intrauterine resuscitation	1	110	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.87, 1.45]
7 Meconium-stained amniotic fluid	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.51, 1.71]
8 Admission to NICU	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.46, 1.89]
9 Postpartum haemorrhage	1	110	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.24, 8.02]

Analysis 8.1. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 1 Caesarean delivery.

Analysis 8.2. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 2 Five-minute Apgar score < 7.

Analysis 8.3. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 3 Umbilical artery pH < 7.0.

Analysis 8.4. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 4 Uterine tachysystole 10 minutes after drug.

Analysis 8.5. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 5 Need for repeat dose of tocolytic.

Analysis 8.6. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 6 Successful fetal intrauterine resuscitation.

Analysis 8.7. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 7 Meconium-stained amniotic fluid.

Analysis 8.8. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 8 Admission to NICU.

Analysis 8.9. Comparison 8 IV terbutaline versus IV nitroglycerin, Outcome 9 Postpartum haemorrhage.

APPENDICES

Appendix 1. ICTRP and ClinicalTrials.gov - search methods

ICTRP

tachysystole

hyperstimulation AND labor

hyperstimulation AND labour

tocolytics AND resuscitation

tocolysis AND resuscitation

ClinicalTrials.gov

Advanced search

Intervention studies | tocolytics | fetal distress

Intervention studies | tachysystole

Intervention studies | hyperstimulation | labor

Intervention studies | hyperstimulation | fetal

Intervention studies | resuscitation | tocolytics

CONTRIBUTIONS OF AUTHORS

Thach Tran wrote the first version of the protocol. Regina Kulier and Justus Hofmeyr critically commented on the drafts.

For the full review, Sebastian Leathersich and Joshua Vogel screened search results for inclusion/exclusion, reviewed and extracted data from the studies and performed risk of bias assessments. Sebastian Leathersich completed the data analyses and wrote the first draft of the manuscript. All authors reviewed, edited and approved the final version of the manuscript.

DECLARATIONS OF INTEREST

Sebastian J Leathersich: none known.

Joshua P Vogel: none known.

Thach Son Tran: has received salary support from [Garvan Institute of Medical Research](#) since July 2014

G Justus Hofmeyr is an author of a trial included in the review ([Kulier 1997](#)). Decisions regarding inclusion of this trial were made by Sebastian Leathersich and Joshua Vogel.

SOURCES OF SUPPORT

Internal sources

- Eastern Cape Department of Health, South Africa.
Salary support for GJH
- Australian Research Centre for Health of Women and Babies, Australia.
Salary support for TST

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some differences between the published protocol of [Tran 2012](#) and the full review - these are listed below.

Sebastian Leathersich and Joshua P Vogel have joined the review team. Sebastian has taken over as the contact person for this review. Regina Kulier is no longer a co-author on this review.

The methods have been updated in line with the standard methods of Cochrane Pregnancy and Childbirth and current Cochrane methodology.

We added an additional search of [ClinicalTrials.gov](#) and the WHO International Clinical Trials Registry Platform for unpublished, planned and ongoing trial reports (ICTRP).

We now include the use of GRADE to assess the quality of the evidence and our assessments are presented in [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#); [Summary of findings 5](#); [Summary of findings 6](#); [Summary of findings 7](#); and [Summary of findings 8](#).

Due to the small number of identified studies, we decided to include abstracts if they met other eligibility criteria.

The cut-off for the secondary outcome of umbilical artery pH was changed from "< 7.0", to "< 7.0 or as defined by the trial authors". This change was made as we found some studies reported a low umbilical artery pH as < 7.1 or < 7.2, which were considered by the review authors to be clinically relevant cut-off values.

We included a definition for the outcome 'postpartum haemorrhage' - blood loss > 500 mL.

We edited the secondary outcome 'base excess/deficit' to 'umbilical cord blood base excess/deficit'.

We changed the secondary outcome "neonatal intensive care unit admission for 24 hours or more" to "neonatal intensive care unit admission", as no included studies reported on the length of admission, and we considered any admission to be clinically relevant.

We included a number of non-prespecified outcomes as we considered them to be both relevant to the clinical questions posed by the review and to reflect prespecified outcomes. These included "no improvement in FHR tracing" ([Kulier 1997](#); [Patriarco 1987](#)), "resolution of fetal distress" ([Magann 1993](#)) and "successful intrauterine fetal resuscitation" ([Pullen 2007](#)), which we considered to be important clinical outcomes when considering the role of acute tocolysis for suspected fetal distress and to reflect the prespecified outcome of "abnormal FHR as defined by the trial authors". We considered the volume of blood loss reported by the [Magann 1993](#) study to be a relevant outcome related to the predetermined outcome of postpartum haemorrhage. Finally, we considered the time taken for uterine hyperstimulation to resolve and the rate of recurrence of uterine hyperstimulation ([Pacheco 2006](#)), to be similar to the predetermined outcome of uterine tachysystole and to be of clinical interest.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-2 Receptor Agonists [therapeutic use]; Cesarean Section [statistics & numerical data]; Fenoterol [therapeutic use]; Fetal Distress [*drug therapy]; Hexoprenaline [therapeutic use]; Nitroglycerin [therapeutic use]; Perinatal Death; Randomized Controlled Trials as Topic; Terbutaline [therapeutic use]; Tocolysis [*methods]; Tocolytic Agents [*therapeutic use]; Uterine Contraction [*drug effects]; Vasotocin [analogs & derivatives] [therapeutic use]

MeSH check words

Female; Humans; Pregnancy